TREATMENT OF TUBERCULOSIS

Annex 5

REPORTS OF THE SYSTEMATIC REVIEWS

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

World Health Organization

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Decentralised Treatment and Care for Multi-Drug Resistant Tuberculosis Patients

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Abbreviations & acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ATS	American Thoracic Society
BMI	body mass index
CDC	United States Centers for Disease Control and Prevention
DOT	directly observed treatment
E	Ethambutol
FDC	fixed-dose combination
GDG	Guideline Development Group
Gfx	Gatifloxacin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	Global TB Programme
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IRIS	Immune Reconstitution Inflammatory Syndrome
KNCV	Royal Dutch Tuberculosis Foundation
MDR-TB	multidrug-resistant tuberculosis
Mfx	Moxifloxacin
NGO	non-governmental organization
PICO	Patients, Intervention, Comparator and Outcomes
RIF or R	Rifampicin
RFP	Rifapentine
SAT	self-administered treatment or unsupervised treatment
SMS	Short Message Service or text message
TB	tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
VOT	video-observed treatment
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Report on Systematic Review for Category II TB Treatment

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Background

Historically, WHO has recommended Category II treatment (2HRZES/1HRZE/5HRE) for tuberculosis (TB) patients with a previous history of treatment with first line anti-TB drugs. A systematic review by Menzies et al (2009) searched the literature from 1965-2008 for studies of patients undergoing retreatment with Category II treatment regimen, with a focus on patients with mono-resistance to isoniazid, and found suboptimal outcomes and significant variability in failure rates.

The present analysis updates this systematic review from 2008 to 2016, and focuses on patient cohorts for whom drug resistance status is unknown. The specific terms of reference were to:

1. Undertake a systematic review and analysis evaluating the following PIO question;
2. Work in close liaison with WHO/Global TB Programme and, where necessary, other contributors to the studies and data in carrying out this work; and invite WHO/GTB technical focal points and others who are significant contributors to be co-authors in subsequent publication of the systematic reviews contracted;
3. Deliver the findings per agreed timelines including submitting the report of findings and presenting the findings at the guideline meeting; and
4. Sign and comply with the confidentiality agreement with WHO for not releasing or publishing results of the systematic reviews prior to the approval of the WHO Guideline Review Committee for the publication of WHO TB treatment guidelines.

All aspects of the terms of reference have been completed, including this final report.

PIO question

For patients with a previous history of treatment with first line anti-TB drugs being considered for retreatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing, does empiric treatment with five first line drugs (2HRZES/1HRZE/5HRE) lead to acceptable outcomes?

Table 1. Description of PIO

Population	Intervention	Outcomes: Critical	Outcomes: Important
TB patients previously treated with 1st line drugs (2HRZE/4HR), with unknown INH and RIF resistance.	2HRZES/1HRZE/5HRE (Category II retreatment regimen)	- Cure - Treatment failure - Relapse - Death	- Acquisition/amplification of drug resistance - Smear or culture conversion - Drug adverse events

Review methodology

The following protocol was developed prior to beginning the systematic review in accordance with the PIO question defined above.

This systematic review was conducted according to the Preferred Reporting for Systematic Review and Meta-Analyses (PRISMA) guidelines, where applicable.

Study selection

We searched Pubmed, Cochrane, and Embase databases between January 1, 2008 and May 17, 2016 with no restriction on language using the following search strategy:

Table 2. Search protocol

Step	Search terms (PubMed)	Search terms (Embase)	Search terms (Cochrane)
1	Tuberculosis[Mesh]	tb[exp]	tb
2	tb	tb	tuberculosis
3	tuberculosis	tuberculosis[exp]	1-2/OR
4	1-3/OR	tuberculosis	retreatment
5	Retreatment[Mesh]	1-4/OR	relapse
6	retreatment	retreatment[exp]	previously treated
7	relapse	retreatment	4-6/OR
8	previously treated	relapse[exp]	3 AND 7
9	5-8/OR	relapse	
10	4 AND 9	previously treated	
11		6-10/OR	
12		5 AND 10	
Date conducted	5/17/16	5/17/16	5/17/16
Results	1677	2278	8

We included randomized controlled trials and cohort studies enrolling previously treated PTB patients initiating WHO Category II retreatment regimen due to TB recurrence or treatment interruption. We excluded studies if there were no bacteriologic outcomes; if participants were only described as "retreatment" patients, with no reference to the WHO Category II regimen; if participants were given modified Category II regimens; if DST was performed in the patient population and results guided patient management or if it was unclear if DST results guided patient management; if there was insufficient data for analysis (e.g. outcomes not stratified by treatment regimen); or if the publication was not in English.

Two reviewers (CRM, LHC) participated in study selection. A single reviewer independently

screened titles and abstracts for relevance. We excluded publications from full text review if they were not about TB or if they definitively met one of the exclusion criteria. A single reviewer independently performed full text reviews to identify publications for inclusion. A single reviewer independently abstracted data using a standardized form. We abstracted data concerning treatment outcomes, acquisition or amplification of drug resistance, and adverse events for patients receiving Category II retreatment due to treatment interruption or TB recurrence (Table 1). When possible, we stratified data by reason for retreatment (treatment interruption or TB recurrence). We assessed study quality using applicable criteria from the Newcasle-Ottowa Scale.

Analysis

We determined the proportion of patients receiving the WHO Category II retreatment regimen who experienced each outcome for each study and pooled data to calculate medians, IQRs, and ranges. When possible, we stratified data by reason for retreatment (treatment interruption or TB recurrence). In addition, we stratified data by country-level MDR TB prevalence among previously treated TB cases (6-11.9% or 12-29.9%) based on WHO country estimates.

Initial TOR included requests for GRADE evidence profiles, as well as meta-regression, subgroup analyses, and assessments of heterogeneity and bias. However, as there were no comparators for analysis, the GDG requested that we provide descriptive summaries of the studies reporting outcomes of Category II regimens, and no GRADE profiles were developed.

Results

Figure 1: Study selection

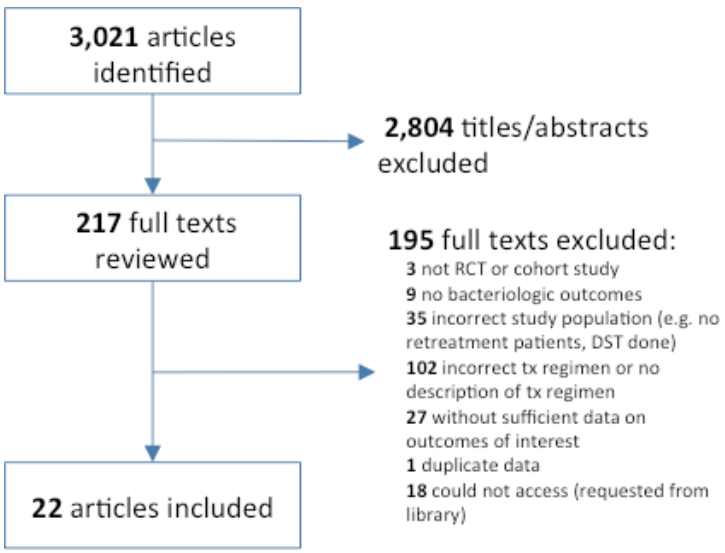

Table 3. Included papers

Author	Year	Country	Study population
Ananthakrishnan [1]	2013	India	TB patients in 12 districts in Tamilnadu, India
Bhagat [2]	2010	India	Retreatment cases at DOTS centers in Nanded, India
Hamusse [3]	2014	Ethiopia	Sm+ cases registered 1997-2011 in Arzi Zone, Central Ethiopia
Huang [4]	2015	China	Outpatients with SS+PTB @ Zhuji hospital from Feb 2011-Oct 2012, new and retreatment
Jones-Lopez [5]	2011	Uganda	Smear- and culture-positive inpatient retreatment cases
Joseph [6]	2011	India	Cat II PTB patients
McGreevy [7]	2012	Haiti	HIV-positive and HIV-negative patients undergoing treatment for recurrent TB with Cat II
Mehra [8]	2008	India	Smear-positive Cat I failures and relapses
Mpagama [9]	2015	Uganda	TB pts
Mukherjee [10]	2009	India	Cat II patients at TB TU
Mukherjee [11]	2015	India	Pediatric retreatment patietns btwn 2004-2012
Mukhopadhyay [12]	2010	India	Retreatment PTB and EPTB cases at TUs in West Bengal, India
Nabukenya-Mudiope [13]	2015	Uganda	Retreatment cases from Jan 1-Dec 31 2010. Only 582 patients treated with Cat II included
Nacef [14]	2011	Algeria	Cat II PTB retreatment patients
Panigatti [15]	2014	India	Children <13 treated for TB in Karnataka hospital, Hubli
Prakasha [16]	2012	India	Retreatment cases at DOTS center
Sarpal [17]	2014	India	Cat II pts registered in RNTCP from June 2010-Dec 2011
Sharma [18]	2008	India	Pediatric pulmonary TB patients (smear-pos tx failures, smear-neg non-responders)
Sharma [19]	2014	India	TB-HIV pts attending ART clinic in North India btwn 2005-2011
Takarinda [20]	2012	Zimbabwe	Adult TB patients registered in district previously treated for TB for >1 month
Wahome [21]	2013	Kenya	Hospital staff
Yoshiyama [22]	2010	Nepal	Retreatment smear-positive TB cases registered at DOTS centers under NTP

The final slide set, stratified by MDR prevalence is provided as companion to this report. This slide set includes the review methodology, included papers, and results.

Slidesets

WHO Category II retreatment

Lelia Chaisson
Cecily Miller
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WHO Guidelines Development Group Meeting
July 2016

PIO question

- For patients with a previous history of treatment with first line anti-TB drugs being considered for retreatment (due to treatment interruption or recurrence) **in the absence of INH and RIF resistance testing**, does empiric treatment with five first line drugs (2HRZES/ 1HRZE/5HRE) lead to acceptable outcomes?

Outcomes of interest

CRITICAL	IMPORTANT
Cure	Acquisition/amplification of drug resistance
Treatment failure	Smear or culture conversion during treatment
Relapse	Drug adverse effects
Death	

Search strategy

- Databases:
  - PubMed:
    - "Tuberculosis"[Mesh] OR tb[All Fields] OR "tuberculosis"[All Fields]) AND ("Retreatment"[Mesh] OR retreatment OR relapse OR "previously treated")
  - Cochrane:
    - (tb OR "tuberculosis") AND (retreatment OR relapse OR "previously treated")
  - Embase:
    - 'tb'/exp OR tb OR 'tuberculosis'/exp OR 'tuberculosis' AND ('retreatment' OR 'retreatment'/exp OR retreatment OR 'relapse'/exp OR relapse OR 'previously treated')
- Dates: January 1, 2008 - May 17, 2016

Study selection

Inclusion criteria

- RCT or cohort study
- Enrolling previously treated PTB patients initiating WHO Cat II retreatment regimen due to TB recurrence or treatment interruption

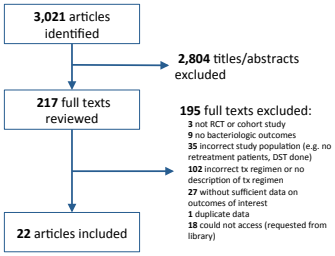
Exclusion criteria

- No bacteriologic outcomes
- Participants only described as "retreatment" patients, with no reference to WHO Cat II regimen
- DST performed in patient population and guided patient management or unclear if guided patient management
- Insufficient data (e.g. outcomes not stratified by treatment regimen)
- Not in English

Methods

- Title/abstract review followed by full-text review (LC, CM)
- Data abstraction (LC, CM)
- Data synthesis
  - Descriptive analysis of treatment outcomes
  - Stratified analyses
    - Country MDR TB prevalence among retreated TB patients
    - Reason for retreatment (relapse/recurrence, treatment interruption)

Systematic review process



Author, year	Country	N	Study population
Nacef, 2011	Algeria	44	PTB relapse patients receiving Cat II treatment
Huang, 2015	China	23	Previously treated smear-positive PTB outpatients receiving Cat II treatment
Hamusse, 2014	Ethiopia	984	Previously treated smear-positive PTB patients receiving Cat II treatment
McGreevy, 2012	Haiti	153	Patients with recurrent TB receiving Cat II treatment
Wahome, 2013	Kenya	46	Hospital staff receiving Cat II treatment
Yoshiyama, 2010	Nepal	242	Previously treated smear-positive TB patients registered at DOTS centers receiving Cat II treatment
Jones-Lopez, 2011	Uganda	288	Previously treated smear- and culture-positive inpatients receiving Cat II treatment
Mpagama, 2015	Uganda	161	Previously treated TB inpatients receiving Cat II treatment
Nabukenya-Mudiope, 2015	Uganda	582	Previously treated TB patients in regional referral hospitals receiving Cat II treatment
Takarinda, 2012	Zimbabwe	135	Adult recurrent TB patients receiving Cat II treatment

Author, year	Country	N	Study population
Mehra, 2008	India	517	Smear-positive Cat I failures and relapses receiving Cat II treatment
Sharma, 2008	India	115	Pediatric pulmonary TB treatment failures placed on Cat II treatment
Mukherjee, 2009	India	234	Cat II patients registered at TB treatment unit
Bhagat, 2010	India	112	Previously treated TB patients at DOTS center receiving Cat II treatment
Mukhopadhyay, 2010	India	212	Previously treated TB treatment failures placed on Cat II treatment
Joseph, 2011	India	74	Previously treated TB patients receiving Cat II treatment
Prakasha, 2012	India	9	Previously treated TB patients registered at DOTS center receiving Cat II treatment
Ananthakrishnan, 2013	India	159	Previously treated TB patients in 12 districts receiving Cat II treatment
Panigatti, 2014	India	4	Previously treated children <13 receiving Cat II treatment
Sarpal, 2014	India	545	Patients receiving Cat II registered in RNTCP
Sharma, 2014	India	23	Previously treated TB-HIV patients attending ART clinic receiving Cat II treatment
Mukherjee, 2015	India	125	Previously treated pediatric patients receiving Cat II treatment

Favorable outcomes

Author	Country	Number retreated	Treatment success		Cure		Treatment completed	
			N	%	N	%	N	%
Nacef	Algeria	44	16	36.4	16	36.4	--	--
Huang	China	23	8	34.8	--	--	--	--
Hamusse	Ethiopia	984	665	67.6	523	53.2	142	14.4
McGreevy	Haiti	153	120	78.4	--	--	--	--
Mehra	India	517	360	69.6	--	--	--	--
Sharma	India	115	95	82.6	80	69.6	15	13.0
Mukherjee	India	234	160	68.4	--	--	--	--
Bhagat	India	112	--	--	--	--	--	--
Mukhopadhyay	India	212	121	57.1	117	55.2	4	1.9
Joseph	India	74	35	47.3	35	47.3	--	--
Prakasha	India	9	8	88.9	--	--	--	--
Ananthakrishnan	India	159	104	65.4	66	41.5	38	23.9
Panigatti	India	3	3	100.0	3	100.0	--	--
Sarpal	India	545	444	81.5	283	51.9	161	29.5
Sharma	India	23	12	52.2	--	--	--	--
Mukherjee	India	125	80	64.0	--	--	--	--
Wahome	Kenya	46	28	60.9	--	--	--	--
Yoshiyama	Nepal	242	138	57.0	138	57.0	--	--
Jones-Lopez	Uganda	288	222	77.1	--	--	--	--
Mpagama	Uganda	161	124	77.0	--	--	--	--
Nabukenya-Mudiope	Uganda	582	322	55.3	--	--	--	--
Takarinda	Zimbabwe	135	102	75.6	--	--	--	--
Range				**36.4-100**		**36.4-100**		**1.9-29.5**
Median				**67.6**		**53.2**		**14.4**

Favorable outcomes

Studies in countries with 6-11.9% prevalence of MDR TB among previously treated TB cases

Author	Country	% retreatment patients with MDR TB (WHO TB report)	Number retreated	Treatment success		Cure		Treatment completed	
				N	%	N	%	N	%
Nacef	Algeria	9.1	44	16	36.4	16	36.4	--	--
McGreevy	Haiti	11	153	120	78.4	--	--	--	--
Takarinda	Zimbabwe	11	135	102	75.6	--	--	--	--
Range					**36.4-78.4**		**36.4**		
Median					**75.6**		**36.4**		

Favorable outcomes

Studies in countries with 12-29.9% prevalence of MDR TB among previously treated TB cases

Author	Country	% retreatment patients with MDR TB (WHO TB report)	Number retreated	Treatment success		Cure		Treatment completed	
				N	%	N	%	N	%
Hamusse	Ethiopia	12	984	665	67.6	523	53.2	142	14.4
Jones-Lopez	Uganda	12	288	222	77.1	--	--	--	--
Mpagama	Uganda	12	161	124	77	--	--	--	--
Nabukenya-Mudiope	Uganda	12	582	322	55.3	--	--	--	--
Wahome	Kenya	14	46	28	60.9	--	--	--	--
Mehra	India	15	517	360	69.6	--	--	--	--
Sharma	India	15	115	95	82.6	80	69.6	15	13
Mukherjee	India	15	234	160	68.4	--	--	--	--
Bhagat	India	15	112	--	--	--	--	--	--
Mukhopadhyay	India	15	212	121	57.1	117	55.2	4	1.9
Joseph	India	15	74	35	47.3	35	47.3	--	--
Prakasha	India	15	9	8	88.9	--	--	--	--
Ananthakrishnan	India	15	159	104	65.4	66	41.5	38	23.9
Panigatti	India	15	3	3	100.0	3	100.0	--	--
Sarpal	India	15	545	444	81.5	283	51.9	161	29.5
Sharma	India	15	23	12	52.2	--	--	--	--
Mukherjee	India	15	125	80	64	--	--	--	--
Yoshiyama	Nepal	15	242	138	57	138	57	--	--
Huang	China	22	23	8	34.8	--	--	--	--
Range					**34.8-100**		**41.5-100**		**1.9-29.5**
Median					**66.5**		**54.2**		**14.4**

Favorable outcomes

Retreatment after relapse

Author	Country	Number retreated	Treatment success		Cure		Treatment completed	
			N	%	N	%	N	%
Hamusse	Ethiopia	867	593	68.4	468	54.0	125	14.4
McGreevy	Haiti	153	120	78.4	--	--	--	--
Mehra	India	390	298	76.4	--	--	--	--
Mukherjee	India	148	113	76.4	--	--	--	--
Prakasha	India	4	--	--	--	--	--	--
Sarpal	India	264	--	--	205	77.7	8	3.0
Mukherjee	India	45	31	68.9	--	--	--	--
Yoshiyama	Nepal	204	118	57.8	118	57.8	--	--
Jones-Lopez	Uganda	150	119	79.3	--	--	--	--
Takarinda	Zimbabwe	103	82	79.6	--	--	--	--
Range				**68.4-79.6**		**54.0-77.7**		**3.0-14.4**
Median				**76.4**		**57.8**		**17.4**

Favorable outcomes

Retreatment after treatment interruption

Author	Country	Number retreated	Treatment success		Cure		Treatment completed	
			N	%	N	%	N	%
Hamusse	Ethiopia	66	38	57.6	26	39.4	12	18.2
Mukherjee	India	34	19	55.9	--	--	--	--
Sarpal	India	75	50	66.7	49	65.3	1	1.3
Mukherjee	India	24	13	54.2	--	--	--	--
Yoshiyama	Nepal	19	9	47.4	9	47.4	--	--
Jones-Lopez	Uganda	129	102	79.1	--	--	--	--
Takarinda	Zimbabwe	32	21	65.6	--	--	--	--
Range				**47.4-79.1**		**39.4-65.3**		**1.3-18.2**
Median				**57.6**		**47.4**		**9.8**

Unfavorable outcomes

Author	Country	Number retreated	Death		Failure		Default	
			N	%	N	%	N	%
Nacef	Algeria	44	--	--	1	2.3	4	9.1
Huang	China	23	--	--	--	--	--	--
Hamusse	Ethiopia	984	115	11.7	15	1.5	189	19.2
McGreevy	Haiti	153	14	9.2	6	3.9	13	8.5
Mehra	India	517	28	5.4	59	11.4	70	13.5
Sharma	India	115	4	3.5	7	6.1	9	7.8
Mukherjee	India	234	14	6.0	31	13.2	26	11.1
Bhagat	India	112	15	13.4	--	--	24	21.4
Mukhopadhyay	India	212	3	1.4	51	24.1	37	17.5
Joseph	India	74	0	0.0	24	32.4	15	20.3
Prakasha	India	9	--	--	--	--	--	--
Ananthakrishnan	India	159	21	13.2	3	1.9	--	--
Panigatti	India	4	0	0.0	0	0.0	0	0.0
Sarpal	India	545	23	4.2	46	8.4	32	5.9
Sharma	India	23	--	--	--	--	--	--
Mukherjee	India	125	0	0.0	20	16.0	25	20.0
Wahome	Kenya	46	--	--	--	--	--	--
Yoshiyama	Nepal	242	3	1.2	13	5.4	17	7.0
Jones-Lopez	Uganda	288	38	13.2	18	6.3	--	--
Mpagama	Uganda	161	21	13.0	4	2.5	12	7.5
Nabukenya-Mudiope	Uganda	582	--	--	--	--	--	--
Takarinda	Zimbabwe	135	6	4.4	0	0.0	9	6.7
Range				**0.0-13.4**		**0.0-32.4**		**0.0-25.0**
Median				**4.9**		**5.8**		**9.1**

Unfavorable outcomes

Studies in countries with 6-11.9% prevalence of MDR TB among previously treated TB cases

Author	Country	% retreatment patients with MDR TB (WHO TB report)	Number retreated	Death		Failure		Default	
				N	%	N	%	N	%
Nacef	Algeria	9.1	44	--	--	1	2.3	4	9.1
McGreevy	Haiti	11	153	14	9.2	6	3.9	13	8.5
Takarinda	Zimbabwe	11	135	6	4.4	0	0.0	9	6.7
Range					**4.4-9.2**		**0.0-3.9**		**6.7-9.1**
Median					**6.8**		**2.3**		**8.5**

Unfavorable outcomes

Studies in countries with 12-29.9% prevalence of MDR TB among previously treated TB cases

Author	Country	% retreatment patients with MDR TB (WHO TB report)	Number retreated	Death		Failure		Default	
				N	%	N	%	N	%
Hamusse	Ethiopia	12	984	115	11.7	15	1.5	189	19.2
Jones-Lopez	Uganda	12	288	38	13.2	18	6.3	--	--
Mpagama	Uganda	12	161	21	13	4	2.5	12	7.5
Nabukenya-Mudiope	Uganda	12	582	--	--	--	--	--	--
Wahome	Kenya	14	46	--	--	--	--	--	--
Mehra	India	15	517	28	5.4	59	11.4	70	13.5
Sharma	India	15	115	4	3.5	7	6.1	9	7.8
Mukherjee	India	15	234	14	6	31	13.2	26	11.1
Bhagat	India	15	112	15	13.4	--	--	24	21.4
Mukhopadhyay	India	15	212	3	1.4	51	24.1	37	17.5
Joseph	India	15	74	0	0	24	32.4	15	20.3
Prakasha	India	15	9	--	--	--	--	--	--
Ananthakrishnan	India	15	159	21	13.2	3	1.9	--	--
Panigatti	India	15	4	0	0.0	0	0.0	0	0.0
Sarpal	India	15	545	23	4.2	46	8.4	32	5.9
Sharma	India	15	23	--	--	--	--	--	--
Mukherjee	India	15	125	0	0	20	16	25	20
Yoshiyama	Nepal	15	242	3	1.2	13	5.4	17	7
Huang	China	22	23	--	--	--	--	--	--
Range					**0.0-13.4**		**0.0-32.4**		**0.0-25.0**
Median					**4.8**		**6.3**		**12.3**

Unfavorable outcomes

Retreatment after relapse

Author	Country	Number retreated	Death		Failure		Default	
			N	%	N	%	N	%
Hamusse	Ethiopia	867	97	11.2	10	1.2	167	19.3
McGreevy	Haiti	153	14	9.2	6	3.9	13	8.5
Mehra	India	390	20	5.1	24	6.2	48	12.3
Mukherjee	India	148	9	6.1	9	6.1	15	10.1
Prakasha	India	4	--	--	--	--	--	--
Sarpal	India	264	12	4.5	23	8.7	16	6.1
Mukherjee	India	45	--	--	--	--	--	--
Yoshiyama	Nepal	204	3	1.5	10	4.9	10	4.9
Jones-Lopez	Uganda	150	22	14.7	7	4.7	--	--
Takarinda	Zimbabwe	103	4	3.9	0	0.0	6	5.8
Range				**1.5-14.7**		**0.0-8.7**		**4.9-19.3**
Median				**5.6**		**4.8**		**8.5**

Unfavorable outcomes

Retreatment after treatment interruption

Author	Country	Number retreated	Death		Failure		Default	
			N	%	N	%	N	%
Hamusse	Ethiopia	66	10	15.2	1	1.5	17	25.8
Mukherjee	India	34	3	8.8	8	23.5	3	8.8
Sarpal	India	75	6	8.0	10	13.3	9	12.0
Mukherjee	India	24	--	--	--	--	--	--
Yoshiyama	Nepal	19	0	0.0	2	10.5	6	31.6
Jones-Lopez	Uganda	129	13	10.1	7	5.4	--	--
Takarinda	Zimbabwe	32	2	6.3	0	0.0	3	9.4
Range				**0.0-15.2**		**0.0-23.5**		**8.8-31.6**
Median				**8.4**		**8.0**		**12.0**

Relapse & acquisition of drug resistance

Author	Country	% retreatment patients with MDR TB (WHO TB report)	Number retreated	Relapse		Acquisition of drug resistance	
				N	%	N	%
Yoshiyama	Nepal	15	242	5	2.1	3	1.2

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Report on Systematic Review for Adherence Interventions in TB Treatment

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Background

The current treatment for drug-susceptible pulmonary tuberculosis (PTB), for most types of extra-pulmonary TB, and for human immunodeficiency virus (HIV) associated TB is a 6-month multidrug regimen. Ensuring adherence to long-duration treatment regimens is challenging and incomplete treatment may lead to poor outcomes including treatment failure, relapse, and acquisition of drug resistance. Several adherence strategies have been implemented over the years to improve adherence with therapy. Perhaps the most commonly known such intervention is directly observed therapy (DOT) introduced in the early 1960s in which a health worker, family member, or community member observes the patient taking TB medications(1). Other interventions have included financial incentives, implementing reminder or tracking systems, improving patient and staff education, and most recently the use of mobile technology for video observed therapy and SMS tracking. The resources necessary for such interventions vary and many centers across the world have been using a combination of these strategies to improve TB treatment outcomes. Here, we set out to determine which of these interventions, alone or in conjunction with a package of interventions, leads to improved TB treatment outcomes.

The specific terms of reference for the current systematic review were as follows.

- Undertake systematic reviews and analysis evaluating the following PICO question: In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the following outcomes: treatment adherence, conventional treatment outcomes, adverse reactions, acquired drug resistance, patient costs and health service costs?
- Work in close liaison with WHO/Global TB Programme and, where necessary, other contributors to the studies and data in carrying out this work; and invite WHO/GTB technical focal points and others who are significant contributors to be co-authors in subsequent publication of the systematic reviews contracted;
- Deliver the findings per agreed timelines including submitting the report of findings and presenting the findings at the guideline meeting; and
- Sign and comply with the confidentiality agreement with WHO for not releasing or publishing results of the systematic reviews prior to the approval of the WHO Guideline Review Committee for the publication of WHO TB treatment guideline.

PICO Question

In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?

Table 1. Breakdown of the PICO question

Population	Intervention	Comparator	Outcome
Patients on treatment for DS-TB Patients on MDR-TB treatment Children (0-14y) and adults HIV-infected and HIV-uninfected TB patients	Any intervention to promote treatment adherence • Supervising treatment (DOT, VOT) • Measures to improve treatment adherence (e.g. medication monitors and/or SMS or phone call reminders) • Social support (educational, psychological, material) • Combinations of the above interventions	Routine practice*	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death • Adverse reactions from TB drugs (severity, type, organ class) • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to health services

* Routine practice: regular TB drugs pick-up and consultations with physician or other health-care workers are available when necessary; TB treatment is free of charge; essential information/health education in relation to TB treatment is provided.

Review methodology

A protocol for this systematic review was generated prior to conducting the literature search and conducted in accordance with the PRISMA guidelines.

All aspects of the terms of reference have been completed, including this final report.

Study Selection

We searched pubmed through February 6th, 2016. Title and abstract review was performed by one reviewer (NA) and full text reviews were done by multiple reviewers. We included all randomized controlled trials, quasi-randomized studies, and prospective or retrospective cohort studies that met the inclusion criteria. Articles were excluded if they were conducted on patients with latent tuberculosis, did not have a current or historical control group, or if the article was not published in English. Two foreign language articles were included as data from them was previously abstracted by a different systematic review. Studies that specifically compared DOT delivered in a hospital setting versus clinic setting were excluded from this review due to a different systematic review dedicated to the comparison being conducted at the time of our review.

Table 2. Search protocol for adherence interventions in TB

Step	Search Terms (Pubmed)
1	TB
2	tuberculosis
3	1 OR 2
4	"directly observed therapy"
5	"directly observed treatment"
6	"supervised therapy"
7	"supervised treatment
8	DOT*
9	VOT
10	"video observed"
11	SMS
12	Text messag*
13	phone
14	telephone
15	Patient adherence
16	video
17	Patient participation
18	motivation
19	Decision support techniques
20	Default*
21	Adheren*
22	Supervis*
23	4-22/OR
24	3 AND 23
Date conducted	12/12/2015
Results	6394
Date search repeated	2/6/2016
Final results	6467

A separate search was conducted for video/SMS interventions in TB through June 28th, 2016 using the following search strategy.

Table 3. Search protocol for SMS/video interventions

Step	Search Terms (Pubmed)
1	TB
2	tuberculosis
3	1 OR 2
4	Text message
5	SMS
6	Cell phone
7	Video
8	4-7/OR
9	3 AND 8
Date conducted	6/28/2016
Results	425

Analysis

The Cochrane risk of bias tool was used to assess the quality of randomized controlled trials (reference) and the Newcastle-Ottawa Scale was used for observational studies (reference). The types of information abstracted from each article included setting, average age of patients enrolled, type of tuberculosis (pulmonary vs extapulmonary), drug resistance, co-infection with HIV, type of adherence intervention, and conventional TB treatment outcomes including cure, success, treatment failure, default or loss to follow up, adverse reactions, and death. The standard WHO definition was used for all outcomes of interest. One reviewer (NA) abstracted all data for analysis. Data was abstracted and analyzed using RevMan. Where two or more studies reported on similar outcomes, data was pooled using random effects meta-analysis. Heterogeneity was assessed using Chi-squared test available in RevMan with p<005 used to determine statistical significance. Where more than 15 studies were available for a particular question, we used funnel plots to determine publication bias.

Results

Characteristics of the included studies are summarized in the tables provided below. The complete slide set is provided as a companion to this report and includes a summary of the methodology as well as forest plots and GRADE evidence profiles for each comparison.

Figure 1. PRISMA diagram

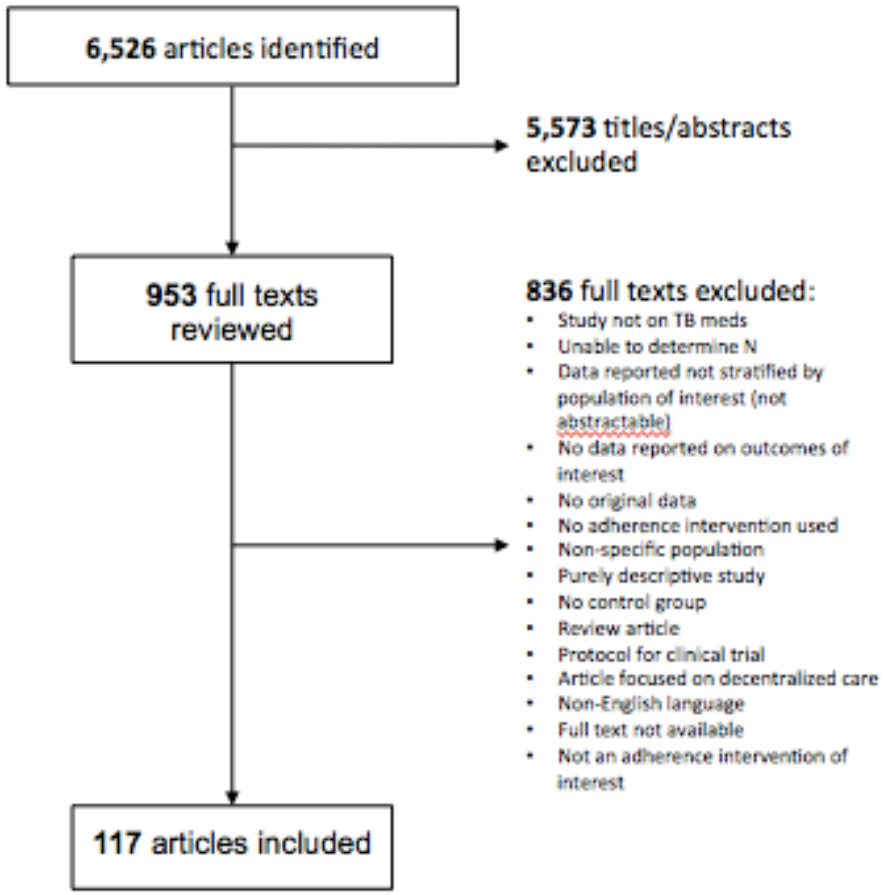


Table 4. Characteristics of included studies: SAT vs DOT

Comparison: Self-administered therapy as an intervention versus directly observed therapy

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Kamolratanakul (2)	1999	RCT	Thailand	836	-PTB (smear +) ->15 years	-Daily -Clinic, community member, Family member
MacIntyre(3)	2003	Quasi-RCT	Australia	173	-Excluded MDR, relapse, HIV+ ->14 years	-Daily -Family member
TRC Chennai(4)	1997	Clinical trial, not rand-omized	India	825	-PTB (smear +) -excluded those who missed >25% of rx. -Included INH/RIF mono-resistant ->12 years	-Twice weekly -Clinic.
Walley(5)	2001	RCT	Pakistan	497	-PTB (smear +) ->15 years	-Daily -Clinic, Home (health worker or family member)
Zwarenstein(6)	1998	RCT	South Africa	216	-PTB (smear +) -Excluded MDR, h/o ATT>2wks ->15 years	-Daily -Clinic
Zwarenstein(7)	2000	RCT	South Africa	156	-PTB (smear +) -Excluded MDR, h/o ATT>2wks ->15 years	-Daily -Clinic, Home (health worker or family member)
Tandon(8)	2002	RCT	India	400	-PTB (smear +) -Excluded HIV+ ->20 years	-Provided by patient attendant or school teacher
Akkslip(9)	1999	Prospective	Thailand	779	-PTB (smear +/-) -EPTB	-DOT, family member or village volunteer
Balasubramanian (10)	2000	Retrospec-tive	India	200	-New -PTB (smear +)	-DOT by health workers -Thrice weekly intensive phase -Once weekly continuation phase
Mathema(11)	2001	Prospective	Nepal	759	-PTB (smear +/-) -EPTB (4%) -Adults & children	-DOT by health workers, community, or family -Intensive phase only, daily
Ormerod(12)	2002	Mixed	UK	205	-PTB (smear +/-) -Adults	-Thrice weekly regimen
Tsuchida(13)	2003	Retrospec-tive	Japan	80	-PTB (smear +) -Excluded DR -New & retreatment -Adults	-Hospital until sputum conversion -Daily DOT by clinic nurse
Nirupa(14)	2005	Retrospec-tive	India	865	-PTB (smear +) -New -Adults & children	-DOT by CHWs, teachers, community volunteers
Daniel(15)	2006	Retrospec-tive	Nigeria	467	-PTB (Smear +/-) -EPTB ->15 years	-No info
Okanurak(16)	2007	Prospective	Thailand	931	-> 15 years	-Clinic, family, community DOT

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Abassi(17)	2007	Prospective	Iran	260	-PTB (smear +) -New	-Clinic DOT
Szczesniak(18)	2009	Retrospective	Poland	100	-PTB (smear +/-) -New	-DOTS (not defined)
Cayla(19)	2009	Prospective	Spain	1490	-PTB (smear +/-) -EPTB ->18 years -No drug resistance -TB/HIV -New & retreatment	-Provided to those at higher risk of default
Zvavamwe(20)	2009	Prospective	Namibia	332	-Post-hospital discharge	-Community or clinic DOT -Continuation phase only
Xu(21)	2009	Prospective	China	670	-PTB (smear +) -Adults -New & retreatment	-DOT by family member, health worker, or village doctor
Abuaku(22)	2010	Retrospective	China	68430	-PTB (smear +/-) -EPTB -Adults & children -New & retreatment	-DOT -Modified DOT (intensive phase only)
Ershova(23)	2014	Retrospective	South Africa	741	-Adults & children -TB/HIV (60%) -PTB (smear +/-) -EPTB -New & retreatment	-Full DOT vs partial DOT
Weis(24)	1995	Retrospective	USA	988	-Adults & children -MDR/TB -TB/HIV (data only available for the DOT group) -PTB -EPTB	-DOT offered at multiple locations, daily for 2-4 wks, then twice weekly for 2-4 wks.
Bashar(25)	2001	Retrospective	USA	28	-Diabetics vs non-diabetics -PTB -TB/HIV -MDR-TB (100%) -Adults & 2 children	-No info
Olle-Goig(26)	2001	Retrospective	Haiti	281	-PTB (smear +/-) -TB/HIV -New & retreatment -EPTB -Adults	-First 2 wks inpatient, rest at home with DOT by HCW -Meds + food delivered twice weekly
Pungrassami(27)	2002	Prospective	Thailand	411	-MDR-TB -TB/HIV -Adults & children	-HCW, community member, or family member DOT
Jasmer(28)	2004	Retrospective	USA	372	-PTB (culture +) -Excluded EPTB -TB/HIV -Adults & children	-DOT + incentives/ enablers -Home, clinic, or workplace
Cayla(29)	2004	Prospective	Spain	1515	-PTB (smear +) -EPTB -TB/HIV -Adults & children	-Provided to those at higher risk of default

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Cavalcante(30)	2007	Retrospective	Brazil	1811	-PTB (smear +/-) -EPTB -TB/HIV -New & retreatment -Adults	-Home or local clinic DOT -CHWs
Radilla-Chavez(31)	2007	Retrospective	Mexico	629	-TB/HIV -New & retreatment -Adults & children -Excluded EPTB	-Daily clinic DOT (intensive phase), thrice weekly continuation phase
Anuwatnonthakate (32)	2008	Prospective	Thailand	8031	-PTB (smear +/-) -TB/HIV -Adults & children -New & retreatment	-HCW or family DOT -Intensive phase only
Kapella(33)	2009	Retrospective	Thailand	791	-Adults & children -TB/HIV -New & retreatment -PTB (smear +/-) -EPTB -MDR-TB	-HCW DOT during intensive phase
Vieira(34)	2011	Retrospective	Brazil	218	-PTB (smear +/-) -EPTB -New & retreatment -Excluded MDR and TB meningoencephalitis -Adults & children -TB/HIV	-Clinic DOT thrice weekly intensive phase, then twice weekly continuation phase
Ong'ang'o(35)	2014	Retrospective	Kenya	2778	-Adults & children -New & retreatment -PTB (smear +/-) -EPTB (24%) -?TB/HIV	-CHW DOT once/wk at home intensive phase, once/month during continuation phase
Mac(36)	1999	Retrospective	USA	50	-Vietnamese ->18 years -PTB (smear +/-) -Excluded TB/HIV, EPTB -MDR-TB	-DOT (no info provided)
Juan(37)	2006	Mixed	Spain	213	-PTB (smear +/-) -EPTB -TB/HIV (70%) -Drug resistant -New & retreatment -Adults & children	-Initial 2 wks inpatient -District based DOT
Chung(38)	2007	Retrospective	Taiwan	399	-PTB (smear +) -Excluded EPTB and MDR/TB -New & retreatment	-Clinic DOT
Yen(39)	2013	Retrospective	Taiwan	3487	->18 years -PTB (smear +/-) -MDR-TB -New & retreatment	-Daily DOT at home or workplace
Chien(40)	2013	Retrospective	Taiwan	2160	-PTB (smear +/-) -M/XDR-TB -Excluded TB/HIV	-DOTS & DOTS-PLUS
Alvarez-Uria(41)	2014	Retrospective	India	1460	-TB/HIV (100%) -PTB (smear +/-) -EPTB except TB meningitis -New & retreatment -Adults	-Inpatient initially -Thrice weekly DOT at hospital

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Das(42)	2014	Retrospective	India	89	-New -PTB (smear +/-) -EPTB -TB/HIV (100%) -Adults	-Daily DOT by CHW at home
Alwood(43)	1994	Retrospective	USA	78	-TB/HIV (100%) -PTB (smear +/-) -Adults -INH and streptomycin resistant (n=1)	-Daily DOT for 9 months

Table 5. Characteristics of included studies: DOT offered by different providers

Comparison: DOT provided by family member, community member, or lay health worker versus DOT provided by healthcare providers

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Mathema(11)	2001	Prospective	Nepal	759	-PTB (smear +/-) -EPTB	-DOT by health workers, community, or family -Intensive phase only, daily
Colvin(44)	2003	Retrospective	South Africa	1816	-PTB (smear +/-) -New & retreatment -EPTB	-DOT by health clinic, CHW, LHW, or traditional healer -First few weeks inpatient
Singh(45)	2004	Retrospective	India	617	-PTB (smear +) -New	-DOT by CHW (gov fscilities) or community volunteer (lay ppl)
Nirupa(14)	2005	Retrospective	India	865	-PTB (smear +) -New	-DOT by CHWs, teachers, community volunteers
Anuwatnonthakate(32)	2008	Prospective	Thailand	8031	-PTB (smear +/-) -TB/HIV -Adults & children -New & retreatment	-HCW or family DOT -Intensive phase only
Kungkaew(46)	2008	Prospective	Thailand	506	-New -PTB (smear +/-) -Adults & children -TB/HIV	-DOT by family member or HCW
Xu(21)	2009	Prospective	China	670	-PTB (smear +)	-DOT by family member, health worker, or village doctor
Tripathy(47)	2013	Retrospective	India	1769	-New -PTB (smear +) -Adults & children	-DOT by community volunteers (CHWs, physicians, alternative medicine doctors, shopkeepers, teachers) vs institutional providers (TB health visitors, staff nurses, auxiliary nurse midlves)
Wilkinson(48)	1997	Retrospective	South Africa	1890	-No info -High HIV prevalent setting	-Choice of HW, CHW, or volunteer lay people. No distinction provided between HW & CHW.

Table 6. Characteristics of included studies: DOT offered at different locations

Comparison: DOT offered at home or in the community versus clinic-based DOT

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Lwilla(49)	2003	RCT	Tanzania	522	-New -PTB (smear +)	-Community based vs institution based DOT
Wandwa-lo(50)	2004	RCT	Tanzania	587	-Adults & children -New -PTB (smear +/-) -EPTB	-Community (family or former TB patient) vs health clinic DOT
Wright(51)	2004	RCT	Swaziland	1353	-Adults & children -PTB (smear +/-) -EPTB -New & retreatment	-DOT by CHW (not at home) vs family member
Newell(52)	2006	RCT	Nepal	907	-PTB (smear +) ->15 years old -New	-Community based DOT vs family member DOT
Akkslip(9)	1999	Prospective	Thailand	779	-PTB (smear +)	DOT, family member or village volunteer
Banerjee(53)	2000	Prospective	Malawi	600	-PTB (smear +/-) -EPTB -New	-DOT at home vs health center vs hospital
Becx-Ble-umink(54)	2001	Prospective	Indonesia	2353	-PTB (smear +) -New	-DOT in community vs clinic -6 times/week DOT by fam member during intensive phase, 5 times/fortnight during continuation phase
Caval-cante(30)	2007	Retrospec-tive	Brazil	1811	-PTB (smear +/-) -TB/HIV -EPTB	-DOT in community (home or church by CHW) vs clinic
Dobler(55)	2015	Retrospec-tive	Mongolia	2181	-PTB (smear +) -> 15 years old	-Daily DOT at home by volunteers -DOT at cafeterias -Clinic DOT
Dudley(56)	2003	Prospective	South Africa	2873	-PTB -EPTB -> 15 years -New & retreatment	-Daily DOT at clinic or community (at CHW's home)
Maciel(57)	2010	Prospective	Brazil	171	-New -TB/HIV -PTB (smear +/-) -EPTB	-Daily DOT by a domiciliary supervisor at home or by CHW at clinic
Miti(58)	2003	Prospective	Zambia	168	-> 15 years -TB/HIV only -New -PTB (smear +)	-Daily DOT delivered at home + AIDS home care program -Daily DOT at clinic
Moalosi(59)	2003	Retrospec-tive	Botswana	633	-TB/HIV -PTB (smear +/-)	-Daily DOT by family at home -Clinic DOT
Niazi(60)	2003	Prospective	Iraq	172	-New -PTB (smear +)	-Daily home vs clinic DOT
Wares(61)	2001	Prospective	Nepal	327	-New & retreatment -PTB (smear +/-) -EPTB	-Daily DOT via health post, clinic, or hostel

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Arora(62)	2003	Prospective	India	2573	-Adults & children -PTB (smear +/-) -EPTB	-DOT by community member at patient's or member's house vs center based DOT
Kironde(63)	2002	Prospective	South Africa	505	-New & retreatment -> 15 years -PTB (smear +)	-Daily clinic or community-based DOT
Van den Boogaard (64)	2009	Retrospec-tive	Tanzania	2769	-Adults & children -New & retreatment -PTB (smear +/-) -EPTB -TB/HIV	-Daily community vs clinic DOT
Manders(65)	2001	Prospective	Malawi	75	-> 18 years -PTB (smear +/-) -EPTB	-Guardian-based (family) DOT vs health-center based vs inpatient
Xu(21)	2009	Prospective	China	670	-PTB (smear +)	-DOT by family member, health worker, or village doctor
Akhtar(66)	2011	Prospective	Pakistan	582	-PTB (smear +) ->15 years -New & retreatment -Excluded drug resistant	-Clinic DOT 5x/wk intensive phase, then 3x/wk continuation phase -Family DOT

Table 7. Characteristics of included studies: Patient education & counseling

Comparison: patient education and counseling in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Clark(67)	2007	RCT	Turkey	114	-New -MDR -Adult	-Oral and written education via clinical pharmacist before d/c -intensive phase inpatient
Janmeja(68)	2004	RCT	India	200	-New -PTB (smear +) -EPTB -Excluded MDR	-Behavioral/psychotherapy at 8 drug collection visits
Liefooghe (69)	1999	RCT	Pakistan	1019	-New -Adults -PTB (smear +/-) -EPTB	-Counseling provided to patients each time they presented for follow up appointment. Also involved social network and family members.
Baral(70)	2014	RCT	Nepal	156	-MDR (100%) -Adults	-Counseling -Counseling plus financial support -None
Dick(71)	1997	Prospec-tive	South Africa	120	-PTB (smear +/-) -> 15 years -Excluded EPTB, MDR -New & retreatment	Oral and written education via clinical pharmacist before d/c

Table 8. Characteristics of included studies: Incentives & enablers

Comparison: Incentives and enablers in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Martins(72)	2009	RCT	East Timor	270	-New -PTB (smear +/-) -Adults	-Daily mid-day food with DOT.
Lutge(73)	2013	RCT	KwaZulu-Natal, South Africa	4,091	New drug-sensitive pulmonary TB, high HIV prevalence	Monthly food voucher on treatment collection
Jahnavi(74)	2010	RCT	India	100	-New ->18 years -PTB (smear +/-) -EPTB -Wasting (BMI <20) -Excluded HIV	-Food supplements and dietary plan -General advice to increase food intake
Sudarsanam (75)	2011	RCT	India	97	->12 years -TB/HIV -New -PTB (smear +/-) -EPTB	-Food supplements & multivitamin vs none
Dobler(55)	2015	Retrospec-tive	Mongolia	2181	-PTB (smear +) -> 15 years old	-Daily DOT at home by volunteers -DOT at cafeterias -Clinic DOT
N-Yanai(76)	2013	Retrospec-tive	Thailand	759	-TB/HIV -Adults & children	-Financial support -Financial support + home visits -None
Zou(77)	2013	Prospective	China	787	-New	-Living subsidy + transport incentive, low SES -Living subsidy + transport incentive, all patients
Lu(78)	2013	Prospective	China	2006	->15 years old -New -PTB	-Transportation subsidies + living allowance
Wei(79)	2012	Prospective	China	183	-PTB (smear +/-) -No EPTB	-Transportation for all -Living allowance for low income patients
Cantalice(80)	2009	Retrospec-tive	Brazil	142	-TB/HIV -PTB (smear +/-) -> 15 years	-Monthly baskets of food
Sripad(81)	2014	Mixed	Ecuador	191	-DR-TB only (including MDR) -TB/HIV -Adults	-Financial bonus after each month of adherence up to 24 months
Tsai(82)	2010	Retrospec-tive	Taiwan	17061	-No info	-Pay for performance
Bock(83)	2001	Retrospec-tive	USA	107	-History of non-adherence -Adults & children -TB/HIV -INH mono-resistant	-Financial incentive

Table 9. Characteristics of included studies: Reminders & tracers

Comparison: Reminders and tracers in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Iribarren(84)	2013	RCT	Argentina	37	-New -Excluded DR or HIV -> 18 years -PTB (smear +)	Patients text daily after taking meds and received reminder texts.
Krishnaswami (85)	1981	RCT	South India	150	-PTB (smear -) -INH mono-resistant (n=3)	SAT, monthly collection. Reminder health visit on 4th day of not picking up meds.
Kunawarak (86)	2011	RCT	Thailand	61	-New -PTB (smear +) ->15 years -TB/HIV -MDR/B (62%) -Excluded XDR/TB	Family-DOT + daily phone call reminder to take meds
Mohan(87)	2003	RCT	Iraq	480	-New -PTB (smear +)	Home visits to patients late for med pick up
Parama-sivan(88)	1993	RCT	India	200	-New -PTB (smear +)	Sent reminder letter to patients late for pick up.
Tanke(89)	1994	Quasi-RCT	USA	2008	-Adults & children -Anyone registered for TB treatment	Automated message reminder before first treatment appointment
Moulding(90)	2002	RCT	Haiti	2002	-> 15 years old -New -PTB (smear +)	-Med monitors with feedback -Med monitors w/o feedback -None
Bronner(91)	2012	Retrospec-tive	South Africa	405673	-PTB (smear +) -New & retreatment -TB/HIV -MDR/TB	-CHWs traced patients who interrupted treatment
Snidal(92)	2015	Prospective	Uganda	142	-> 18 years -PTB (smear +/-) -New & retreatment -TB/HIV -EPTB	-Computer system to ensure CHWs see all patients and keep visit logs
Thomson(93)	2011	Retrospec-tive	Kenya	1369	-TB/HIV (100%) -PTB -Adults & children	-Social worker traced people who missed scheduled clinic appointments
Al-Hajjaj(94)	2000	Retrospec-tive	Saudi Arabia	628	-New & retreatment -PTB -EPTB	-Phone call, then home visit for missed appointments

Table 10. Characteristics of included studies: Mixed interventions

Comparison: Combination package of adherence interventions versus curative therapy alone

Author	Year	Study design	Country	# of patients	Population	Intervention
Khortwong (95)	2013	Qua-si-RCT	Thailand	100	-Undocumented migrant -New TB cases ->70% smear positive	-DOT + patient education and monthly home visits vs DOT alone
Morisky(96)	1990	RCT	USA	88	-New -> 18 years	-Health education and $10 voucher at each monthly visit and $40 if no missed treatment vs monthly clinic follow up alone
Baral(70)	2014	RCT	Nepal	156	-MDR-TB -Adults	-Counseling + financial incentive ($28/mo) q2-3 wks vs none
Drabo(97)	2009	RCT	Burkina Faso	333	-PTB (smear +)	-Food + home visit +psychosocial support vs SAT
Thiam(98)	2007	RCT	Senegal	1522	-Adults -PTB (smear +) -New	-Counseling, choice of DOT supporter, and reinforcement activities vs clinic based DOT
Hsieh(99)	2008	RCT	Taiwan	96	-> 18 years -Excluded EPTB	-DOT in intensive phase, home visit continuation phase and health education -Control: initial ward care followed by monthly clinic follow up
Atkins(100)	2011	Prospec-tive	South Africa	5833	-> 18 years old -PTB (smear +/-) -EPTB -New & retreatment -TB/HIV (>50%) -Excluded M/XDR-TB	-Enhanced DOT with staff training, treatment supporters, and counseling vs standard DOT
Farmer(101)	1991	Prospec-tive	Haiti	60	-PTB -EPTB -TB/HIV	-Daily home visits, monthly reminder visits, food, financial incentive vs SAT
Jasmer (102)	2004	Retro-spective	USA	372	-PTB (culture +) -Excluded EPTB -TB/HIV -Adults & children	-DOT + incentives/enablers at home, clinic, or workplace vs SAT
Soares(103)	2013	Prospec-tive	Brazil	2623	-Adults & children -PTB (smear +/-) -EPTB -New & retreatment -TB/HIV	-DOT + psychosocial intervention + counseling and education + food incentives vs SAT
Yassin(104)	2013	Prospec-tive	Ethiopia	5090	-PTB (smear +/-) -EPTB -Adults & children	-Hospital capacity strengthening, staff education, mobile phone for HCWs, home-based DOT vs clinic/community based DOT
Chan(105)	2013	Retro-spective	Taiwan	390	-MDR-TB (100%) -PTB -New & retreatment -Adults	-Home DOT + incentives/ enablers, optional inpatient component vs hospital and then clinic DOT.
Garden(106)	2012	Prospec-tive	Russia	518	-Adults -New & retreatment (77%) -PTB (smear +/-)	-DOT + food incentive, psychosocial support vs SAT
David-son(107)	1998	Retro-spective	USA	319	-Adults & children -TB/HIV -EPTB -PTB -MDR-TB	-Clinic or home DOT, 5 x/wk, intensive phase, included food coupons, bus tokens vs SAT

Table 11. Characteristics of included studies: Psychosocial interventions.

Comparison: Psychosocial interventions in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Shin(108)	2013	RCT	Russia	196	-> 18 years old -TB/HIV -New & retreatment	Brief counseling intervention for ETOH cessation
Alvarez(109)	2003	RCT	Mexico	87	->15 years old -PTB	Self-help groups
Demissie (110)	2003	Prospective	Ethiopia	128	-Adults & children -PTB (smear +/-)	TB clubs as a support network

Table 12. Characteristics of included studies: Staff education.

Comparison: Staff education in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Lewin(111)	2005	RCT	South Africa	1177	->14 years -PTB (smear +) -New -Excluded MDR-TB	-Adherence education for staff
Ritchie(112)	2015	RCT	Malawi	178	-New -Adults & children -PTB -EPTB -TB/HIV (45%)	-Peer training of LHW -Laminated chart/visual reminder to initiate adherence discussions
Datiko(113)	2009	RCT	Ethiopia	318	-New -PTB (smear +) -Adults & children	-Education for HCW and lab techs
Safdar(114)	2011	Prospective	Pakistan	194	-Children (100%) -PTB (smear +/-) -EPTB	-Staff educational tool and desktop aid for decision making and red flags

Table 13. Characteristics of included studies: Mobile health interventions

Comparison: Use of mobile health interventions in addition to curative therapy versus curative therapy alone

Author	Year	Study design	Country	# of patients	Condition	Intervention
Iribarren(84)	2013	RCT	Argentina	37	-New -> 18 years -PTB (smear +)	Patients text daily after taking meds and received reminder texts.
Kunawarak (86)	2011	RCT	Thailand	61	-New -PTB (smear +)	Family-DOT + daily phone call reminder to take meds
Liu(115)	2015	RCT	China	4173	-New -PTB (smear +/-) -> 18 years	-SMS -Med monitor -Both -Control
Chuck(116)	2016	Prospective	USA	390	->18 years -PTB (smear +/-) -Included drug resistant -Included TB-HIV	-VDOT vs in-person DOT
Broomhead (117)	2012	Case-control	South Africa	120	-PTB (smear +) -New	-Wireless pill box with alarm system sends SMS -DOTS
Wade(118)	2012	Retrospective	Australia	128	-Anyone receiving DOT	-home videophone DOT vs in-person DOT

Table 14.1 Summary of meta-analysis findings of all included adherence interventions

	SAT vs DOT (all)	SAT vs DOT (TB/HIV)	DOT provider-family/community vs HCW	DOT provider-lay provider vs HCW	DOT location-home/community vs clinic	Patient education vs curative therapy alone	Incentives/enablers vs curative therapy alone	Reminders/tracers vs curative therapy alone
Mortality-cohorts	No effect[1]	--[2]	No effect	No effect	No effect	--	↓[3]	No effect
Mortality-RCTs	No effect	--	--	--	No effect	No effect	No effect	No effect
Success-cohorts	↓	↓	No effect	No effect	No effect	--	↑[4]	No effect
Success-RCTs	↓	--	--	--	↑	No effect	↑	↑
Completion-cohorts	No effect	↓	No effect	--	No effect	--	No effect	↑
Completion-RCTs	No effect	--	--	--	↑	↑	↑	No effect
Cure-cohorts	↓	↓	No effect	No effect	No effect	--	↑	No effect
Cure- RCTs	No effect	--	--	--	No effect	↑	No effect	No effect
Failure-cohorts	No effect	↑	No effect	No effect	No effect	--	No effect	No effect
Failure-RCTs	No effect	--	--	--	No effect	No effect	↓	--
Loss to follow up-cohorts	↑	--	↑	No effect	↓	--	No effect	No effect
Loss to follow up-RCTs	↑	--	--	--	No effect	No effect	↓	No effect
Relapse-cohorts	No effect	No effect	--	--	--	--	--	--
Relapse-RCTs	No effect	--	--	--	--	--	--	--
Adherence-Cohorts	↓	--	↓	--	No effect	↑	--	--
Adherence-RCTs	No effect	--	--	--	--	↑	--	↑
Smear conversion-cohorts	No effect	--	--	--	↑	--	--	--
Smear conversion-RCTs	↓	--	--	--	No effect	--	↑	↑
Acquisition of drug resistance-cohorts	↑	--	--	--	--	--	--	↓
Acquisition of drug resistance-RCTs	No effect	--	--	--	--	--	No effect	--
Unfavorable outcome-cohorts	--	--	--	--	↓	--	--	--

1 No effect: There is no statistically significant difference in the rate of outcome occurrence between the intervention and control groups.

2 -- : No outcome data available for the comparison.

3 ↓: Overall estimate of effect shows a significantly lower rate of outcome occurrence in the intervention group compared to the control group.

4 ↑: Overall estimate of effect shows a significantly higher rate of outcome occurrence in the intervention group compared to the control group.

Table 14.2 Summary of meta-analysis findings of all included adherence interventions

	Mixed interventions/ Enhanced DOT vs SAT	Mixed interventions/ Enhanced DOT vs DOT	Mixed case management/ Mixed interventions vs SAT	Psychosocial interventions vs curative therapy alone	Staff education vs curative therapy alone	Phone reminders vs no reminders	VOT vs in-person DOT
Mortality-cohorts	No effect	No effect	--	No effect	No effect	No effect	No effect
Mortality-RCTs	--	↓	No effect	--	No effect	--	--
Success-cohorts	↑	↑	--	--	↑	--	--
Success-RCTs	↑	↑	--	No effect	No effect	No effect	--
Completion-cohorts	↑	No effect	--	↑	--	No effect	No effect
Completion-RCTs	↑	No effect	--	↑	No effect	↓	--
Cure-cohorts	↑	No effect	--	--	--	↑	--
Cure-RCTs	↑	↑	--	No effect	No effect	↑	--
Failure-cohorts	No effect	No effect	--	No effect	No effect	--	--
Failure-RCTs	--	No effect	No effect	↓	No effect	↓	--
Loss to follow up-cohorts	No effect	No effect	--	↓	↓	↓	--
Loss to follow up-RCTs	--	↓	↓	No effect	No effect	--	--
Relapse-cohorts	No effect	--	--	--	--	--	--
Relapse-RCTs	--	--	--	--	--	--	--
Adherence-Cohorts	--	--	--	--	--	--	--
Adherence-RCTs	--	No effect	No effect	--	--	--	--
Smear conversion-cohorts	--	--	--	--	--	↑	--
Smear conversion-RCTs	↑	--	--	--	--	No effect	--
Acquisition of drug resistance-cohorts	No effect	--	--	--	--	--	--
Acquisition of drug resistance-RCTs	--	--	--	--	--	--	--
Unfavorable outcome-cohorts	--	--	--	--	--	↓	--
Unfavorable outcome-RCTs	--	--	--	--	--	--	--
Poor adherence-cohorts	--	--	--	--	--	↓ (phone reminder and med monitor combined)	--

Slidesets

Adherence interventions in TB Treatment

Narges Alipanah, Leah Jarlsberg, Cecily Miller, Andrew Lechner, Kathy Wai, Payam Nahid

UCSF

1

PICO Question

- In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?

2

PICO Question

Population	Intervention	Comparator	Outcome
Patients on treatment for DS-TB Patients on MDR-TB treatment Children (0-14y) and adults HIV-infected and HIV-uninfected TB patients	Any intervention to promote treatment adherence: • Supervising treatment (DOT, VOT) • Measures to improve treatment adherence (e.g. medication monitors and/or SMS or phone call reminders) • Social support (educational, psychological, material) • Combinations of the above interventions	Routine practice	Adherence to treatment (or treatment interruption due to non-adherence) Conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death Adverse reactions from TB drugs (severity, type, organ class) Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) Cost to health services

3

Eligibility

- Study designs:
  - RCTs
  - Prospective and retrospective cohort studies
  - Current or historical control

4

Outcomes of interest

CRITICAL	IMPORTANT
Adherence	Adverse reactions from TB drugs
Cure/completion	Cost to the patient
Failure	Cost to health services
Relapse	
Survival (or death)	
Acquisition (amplification) of drug resistance	
Loss to follow up	

5

Search methods

- Medline database
- Search through 2/6/16
- Title and abstract review by one reviewer
- Full text review by multiple reviewers

6

Analysis

- Data abstraction by one reviewer
- Cochrane risk of bias tool for RCTs
- Newcastle-Ottawa Scale for cohort studies
- Data synthesis in Rev-Man
  - Pool estimates if ≥ 2 studies
  - Random effects meta-analysis

7

Newcastle Ottawa Scale

- 9 point scale:
  - Selection (4)
    - Representativeness of exposed cohort
    - Selection of non-exposed cohort
    - Ascertainment of exposure
    - Demonstration that outcome of interest was not present at start of study
  - Comparability (2)
    - Comparability of cohorts on the basis of design or analysis
  - Outcome (3)
    - Assessment of outcome
    - Length of follow up long enough to ensure outcome occurrence
    - Adequacy of follow up of cohorts

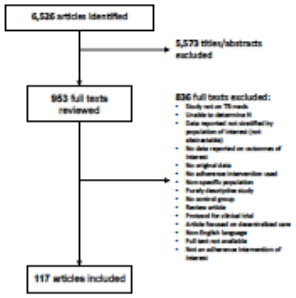
8

Adherence interventions

- SAT vs DOT
- DOT provider
- DOT location
- Reminders & tracers
- Incentives & enablers
- Patient education & counseling
- Mixed case management
- Mobile health (SMS, VOT)
- Psychosocial
- Staff education

9

PRISMA Summary



10

SAT vs DOT

11

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Kamolratanakul	1999	RCT[1]	Thailand	836	-PTB (smear +) -≥15 years	-Daily -Clinic, community member, Family member
MacIntyre	2003	Quasi-RCT[2]	Australia	173	-Excluded MDR, relapse, HIV+ -≥14 years	-Daily -Family member
TRC Chennai	1997	Clinical trial, not randomized[3]	India	825	-PTB (smear +) -excluded those who missed >25% of rx. -included INH/RIF mono-resistant -≥12 years	-Twice weekly -Clinic.
Walley	2001	RCT	Pakistan	497[4]	-PTB (smear +) -≥15 years	-Daily -Clinic, Home (health worker or family member)
Zwarenstein	1998	RCT[5]	South Africa	216[6]	-PTB (smear +) -Excluded MDR, h/o ATT>2wks -≥15 years	-Daily -Clinic
Zwarenstein	2000	RCT[7]	South Africa	156[8]	-PTB (smear +) -Excluded MDR, h/o ATT>2wks -≥15 years	-Daily -Clinic, Home (health worker or family member)

SAT vs DOT 12

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Tandon	2002	RCT	India	400	-PTB (smear +) -Excluded HIV+ -≥10 years	-Provided by patient attendant or school teacher

SAT vs DOT 13

Observational studies

Author	Year	Study design	Country	N	Condition	DOT administration
Akkslip	1999	Prospective	Thailand	779	-PTB (smear +/-) -EPTB	-DOT, family member or village volunteer
Balasubramanian	2000	Retrospective	India	200	-New -PTB (smear +)	-DOT by health workers -Thrice weekly intensive phase -Once weekly continuation phase
Mathema	2001	Prospective	Nepal	759	-PTB (smear +/-) -EPTB (4%) -Adults & children	-DOT by health workers, community, or family -Intensive phase only, daily
Ormerod	2002	Mixed	UK	205	-PTB (smear +/-) -Adults	-Thrice weekly regimen
Tsuchida	2003	Retrospective	Japan	80	-PTB (smear +) -Excluded DR -New & retreatment -Adults	-Hospital until sputum conversion -Daily DOT by clinic nurse
Nirupa	2005	Retrospective	India	865	-PTB (smear +) -New -Adults & children	-DOT by CHWs, teachers, community volunteers
Daniel	2006	Retrospective	Nigeria	467	-PTB (Smear +/-) -EPTB -≥15 years	-No info

SAT vs DOT 14

Observational studies

Author	Year	Study design	Country	N	Condition	DOT administration
Okanurak	2007	Prospective	Thailand	931	-≥15 years	-Clinic, family, community DOT
Abasi	2007	Prospective	Iran	260	-PTB (smear +) -New	-Clinic DOT
Szczesniak	2009	Retrospective	Poland	100	-PTB (smear +/-) -New	-DOTS (not defined)
Cayla	2009	Prospective	Spain	1490	-PTB (smear +/-) -EPTB -≥18 years -No drug resistance -TB/HIV -New & retreatment	-Provided to those at higher risk of default
Zvavamwe	2009	Prospective	Namibia	332	-Post-hospital discharge	-Community or clinic DOT -Continuation phase only
Xu	2009	Prospective	China	670	-PTB (smear +) -Adults -New & retreatment	-DOT by family member, health worker, or village doctor
Abuaku	2010	Retrospective	China	68430	-PTB (smear +/-) -EPTB -Adults & children -New & retreatment	-DOT -Modified DOT (intensive phase only)

SAT vs DOT 15

Observational studies – TB/HIV

Author	Year	Study design	Country	N	Condition	DOT administration
Alwood	1994	Retrospective	USA	78	-TB/HIV (100%) -PTB (smear +/-) -Adults -INH and streptomycin resistant (n=1)	-Daily DOT for 9 months
Das	2014	Retrospective	India	89	-New -PTB (smear +/-) -EPTB -TB/HIV (100%) -Adults	-Daily DOT by CHW at home
Alvarez-Uria	2014	Retrospective	India	1460	-TB/HIV (100%) -PTB (smear +/-) -EPTB except TB meningitis -New & retreatment -Adults	-Inpatient initially -Thrice weekly DOT at hospital
Juan	2006	Mixed	Spain	213	-PTB (smear +/-) -EPTB -TB/HIV (70%) -Drug resistant -New & retreatment -Adults & children	-Initial 2 wks inpatient -District based DOT

SAT vs DOT 16

Observational studies – TB/HIV

Author	Year	Study design	Country	N	Condition	DOT administration
Enthova	2014	Retrospective	South Africa	741	-Adults & children -TB/HIV (60%) -PTB (smear +/-) -EPTB -New & retreatment	-Full DOT vs partial DOT
Weis	1995	Retrospective	USA	988	-Adults & children -MDR/TB -TB/HIV (data only available for the DOT group) -PTB -EPTB	-DOT offered at multiple locations, daily for 2-4 wks, then twice weekly for 2-4 wks.
Bashar	2001	Retrospective	USA	28	-Diabetics vs non-diabetics -PTB -TB/HIV -MDR-TB (100%) -Adults & 2 children	-No info
Olle-Goig	2001	Retrospective	Haiti	281	-PTB (smear +/-) -TB/HIV -New & retreatment -EPTB -Adults	-First 2 wks inpatient, rest at home with DOT by HCW -Meals + food delivered twice weekly

SAT vs DOT 17

Observational studies – TB/HIV

Author	Year	Study design	Country	N	Condition	DOT administration
Pungrassami	2002	Prospective	Thailand	411	-MDR-TB -TB/HIV -Adults & children	-HCW, community member, or family member DOT
Jasmer	2004	Retrospective	USA	372	-PTB (culture +) -Excluded EPTB -TB/HIV -Adults & children	-DOT + incentives/enablers -Home, clinic, or workplace
Cayla	2004	Prospective	Spain	1515	-PTB (smear +) -EPTB -TB/HIV -Adults & children	-Provided to those at higher risk of default
Cavalcante	2007	Retrospective	Brazil	1811	-PTB (smear +/-) -EPTB -TB/HIV -New & retreatment -Adults	-Home or local clinic DOT -CHWs
Radilla-Chavez	2007	Retrospective	Mexico	629	-TB/HIV -New & retreatment -Adults & children -Excluded EPTB	-Daily clinic DOT (intensive phase), thrice weekly continuation phase

SAT vs DOT 18

Quality – Obs

	Selection	Comparability	Outcome
Bashar	3	0	3
Ceyla 2004	4	2	3
Ceyla 2009	4	2	3
Nirupa	3	0	0
Juan	4	2	2
Abuaku	4	2	3
Abassi	3	0	3
Alvarez-Uria	4	2	1
Kapella	4	2	3
Tian	4	2	3
Chien	4	0	3
Ong'ang'o	4	2	3
Enshova	3	0	2
Yen	4	2	3
Das	3	0	3

Newcastle Ottawa Scale

SAT vs DOT 25

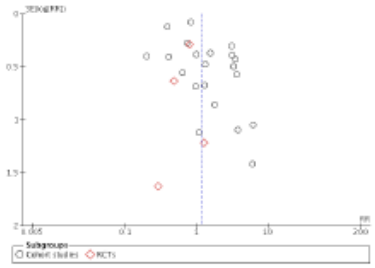
Quality – Obs

	Selection	Comparability	Outcome
Radilla-Chavez	4	0	3
Chung	4	2	3
Daniel	3	0	3
Alwood	4	0	2
Mac	4	2	3
Vieira	4	1	3
Weis	4	0	3

Newcastle Ottawa Scale

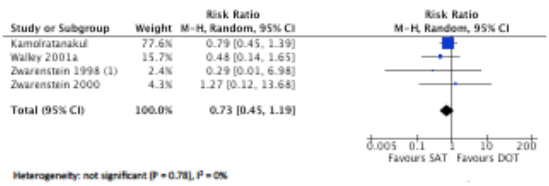
SAT vs DOT 26

Mortality



SAT vs DOT 27

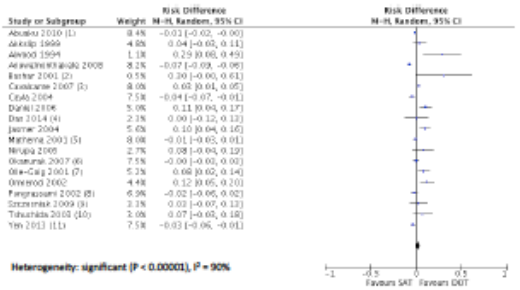
Mortality – RCTs



Heterogeneity: not significant (P = 0.78), I² = 0%

SAT vs DOT 28

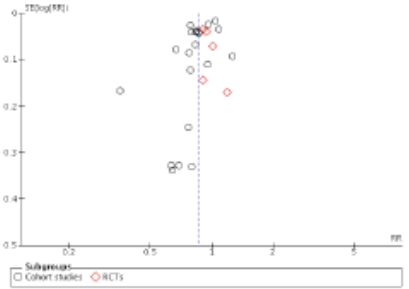
Mortality – Obs



Heterogeneity: significant (P < 0.00001), I² = 90%

SAT vs DOT 29

Treatment success



SAT vs DOT 30

Quality – Obs

	Selection	Comparability	Outcome
Bashar	3	0	3
Ceyla 2004	4	2	3
Ceyla 2009	4	2	3
Nirupa	3	0	0
Juan	4	2	2
Abuaku	4	2	3
Abassi	3	0	3
Alvarez-Uria	4	2	1
Kapella	4	2	3
Tian	4	2	3
Chien	4	0	3
Ong'ang'o	4	2	3
Enshova	3	0	2
Yen	4	2	3
Das	3	0	3

Newcastle Ottawa Scale

SAT vs DOT 25

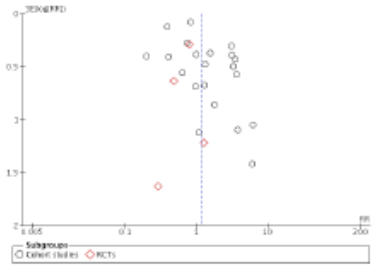
Quality – Obs

	Selection	Comparability	Outcome
Radilla-Chavez	4	0	3
Chung	4	2	3
Daniel	3	0	3
Alwood	4	0	2
Mac	4	2	3
Vieira	4	1	3
Weis	4	0	3

Newcastle Ottawa Scale

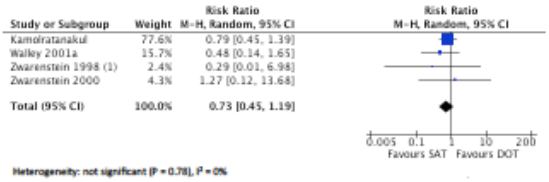
SAT vs DOT 26

Mortality



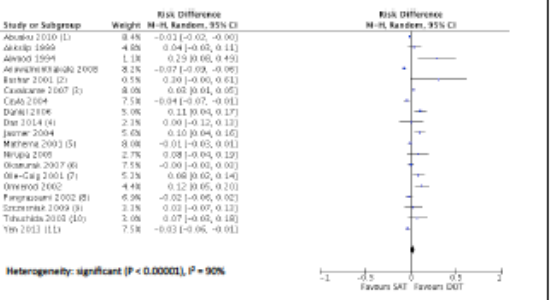
SAT vs DOT 27

Mortality – RCTs



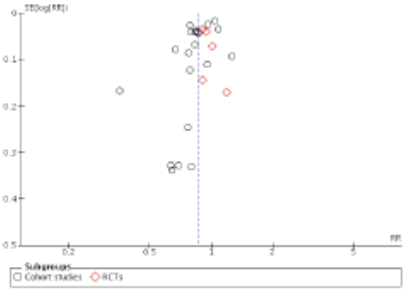
SAT vs DOT 28

Mortality – Obs



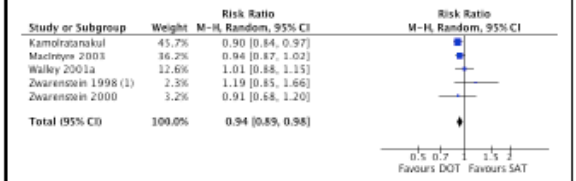
SAT vs DOT 29

Treatment success

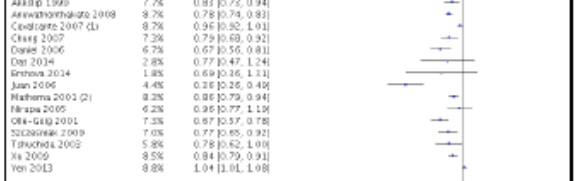


SAT vs DOT 30

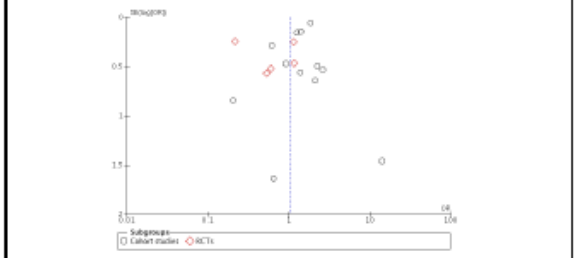
Success - RCTs



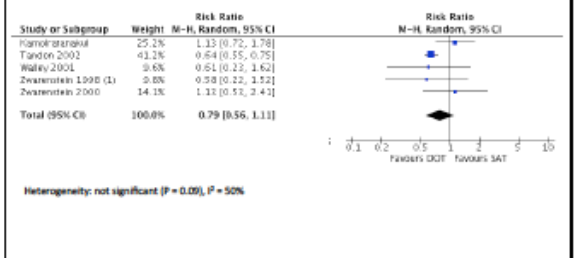
Success – Obs



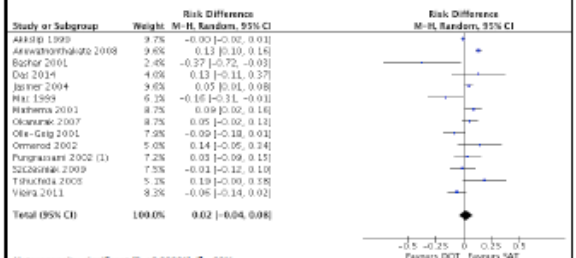
Treatment completion



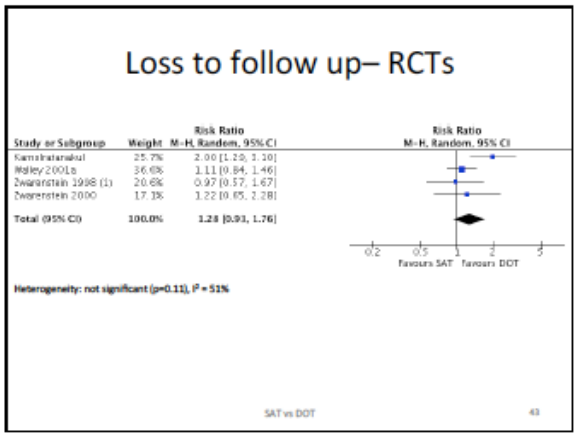
Completion - RCTs

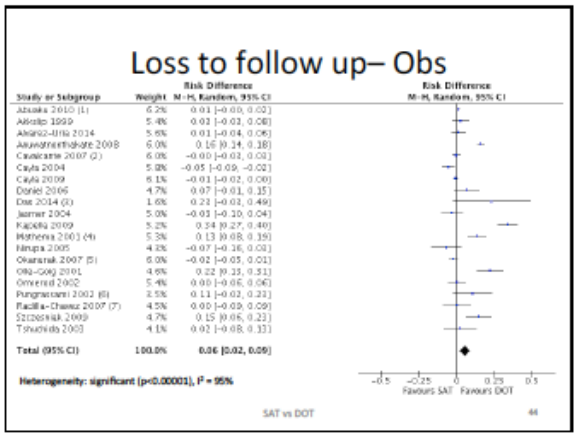


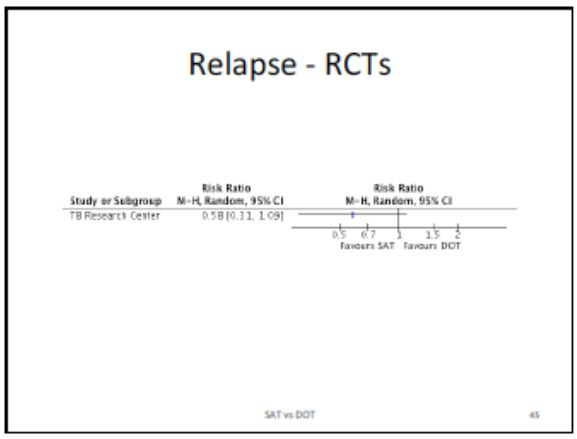
Completion – Obs

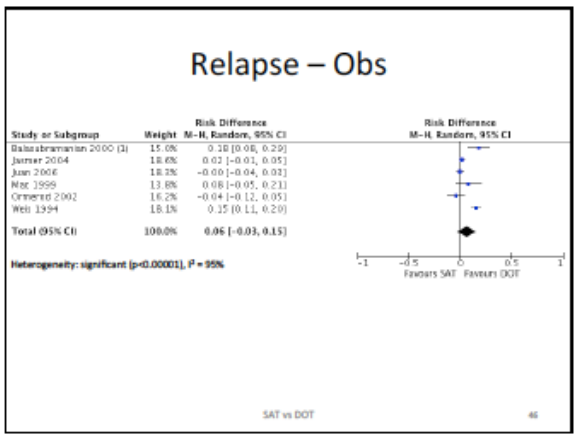


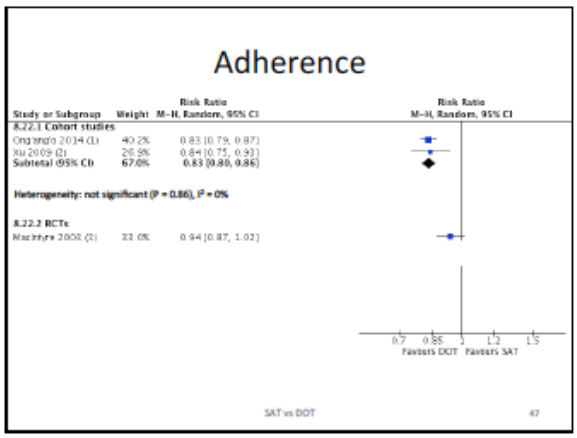
Cure

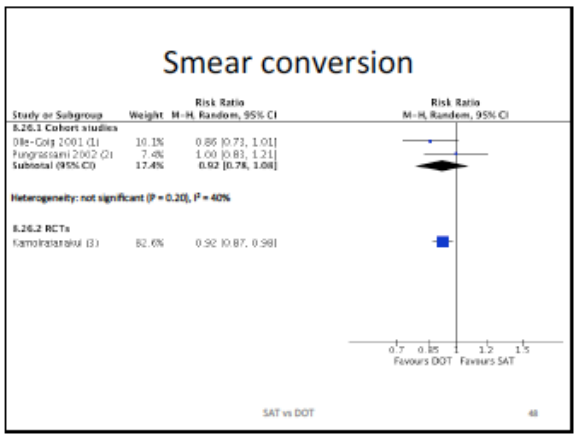

Loss to follow up– RCTs
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Risk Ratio
M-H, Random, 95% CI
Kamolratanakul 25.7% 2.00 [1.26, 3.16]
Walley 2001b 36.6% 1.11 [0.84, 1.46]
Zwarenstein 1998 (1) 20.6% 0.97 [0.57, 1.67]
Zwarenstein 2000 17.1% 1.22 [0.65, 2.28]
Total (95% CI) 100.0% 1.28 [0.93, 1.76]
0.2 0.5 1 2 5
Favours SAT Favours DOT
Heterogeneity: not significant (p=0.11), I² = 51%
SAT vs DOT
43

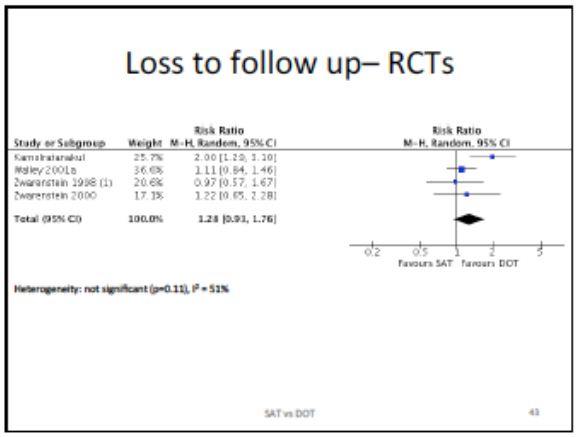

Loss to follow up– Obs
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
Risk Difference
M-H, Random, 95% CI
Akksilp 2009 5.2% 0.24 [0.27, 0.40]
Mathema 2003 (4) 5.2% 0.13 [0.08, 0.19]
Ningsih 2005 4.3% -0.07 [-0.16, 0.02]
Okwera 2007 (5) 6.0% -0.02 [-0.05, 0.01]
Ong-Golz 2001 4.6% 0.22 [0.13, 0.31]
Ormerod 2002 5.4% 0.00 [-0.06, 0.06]
Pungrassami 2002 (6) 3.5% 0.11 [-0.02, 0.23]
Padilla-Chavez 2007 (7) 4.5% 0.00 [-0.09, 0.09]
Szczesniak 2009 4.7% 0.15 [0.06, 0.23]
Tshovhdy 2003 4.1% 0.02 [-0.08, 0.13]
Total (95% CI) 100.0% 0.06 [0.02, 0.09]
-0.5 -0.25 0 0.25 0.5
Favours SAT Favours DOT
Heterogeneity: significant (p<0.00001), I² = 95%
SAT vs DOT
44

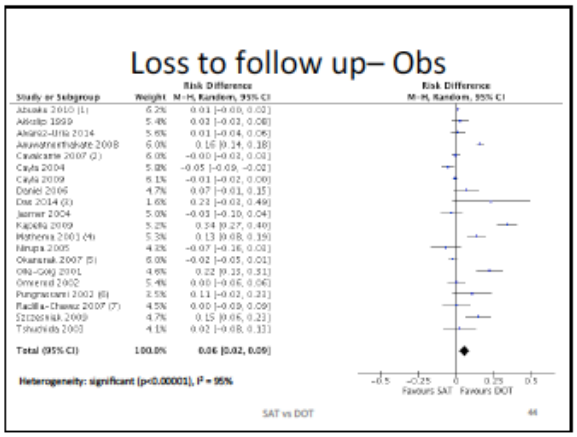

Relapse - RCTs
Risk Ratio
Study or Subgroup M-H, Random, 95% CI
Risk Ratio
M-H, Random, 95% CI
TB Research Center 0.58 [0.31, 1.09]
0.5 0.7 1 1.5 2
Favours SAT Favours DOT
SAT vs DOT
45

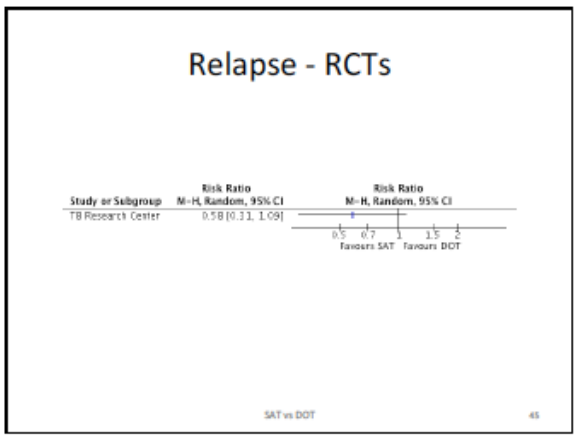

Relapse – Obs
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
Risk Difference
M-H, Random, 95% CI
Balasubramanian 2000 (3) 15.0% 0.18 [0.08, 0.29]
Jasmer 2004 18.6% 0.02 [-0.01, 0.05]
Jiao 2006 18.3% -0.00 [-0.04, 0.03]
Moz 1999 13.8% 0.08 [-0.05, 0.21]
Ormerod 2002 16.2% -0.04 [-0.12, 0.05]
Wei 1994 18.1% 0.15 [0.11, 0.20]
Total (95% CI) 100.0% 0.06 [-0.03, 0.15]
-1 -0.5 0 0.5 1
Favours SAT Favours DOT
Heterogeneity: significant (p<0.00001), I² = 95%
SAT vs DOT
46

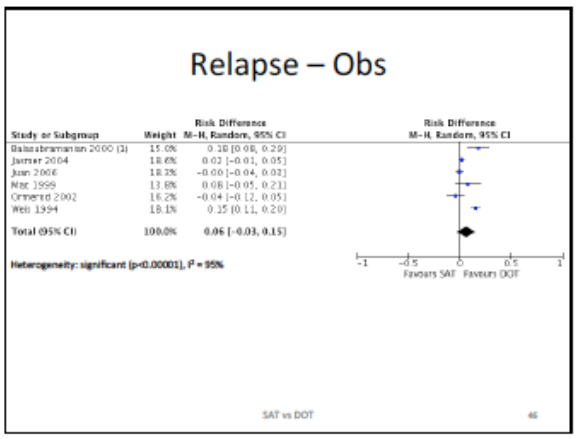

Adherence
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Risk Ratio
M-H, Random, 95% CI
8.22.1 Cohort studies
Ong-Golz 2014 (1) 40.2% 0.83 [0.79, 0.87]
Xu 2009 (2) 26.9% 0.84 [0.75, 0.93]
Subtotal (95% CI) 67.0% 0.83 [0.80, 0.86]
Heterogeneity: not significant (P = 0.86), I² = 0%
8.22.2 RCTs
MacIntyre 2008 (2) 33.0% 0.94 [0.87, 1.02]
0.7 0.85 1 1.2 1.5
Favours DOT Favours SAT
SAT vs DOT
47

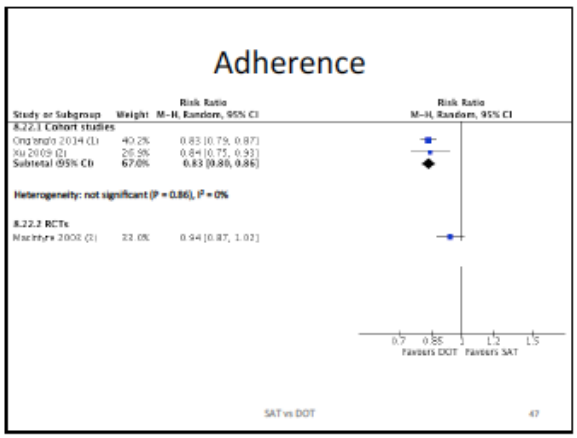

Smear conversion
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Risk Ratio
M-H, Random, 95% CI
8.26.1 Cohort studies
Ong-Golz 2001 (1) 10.1% 0.86 [0.73, 1.01]
Pungrassami 2002 (2) 7.4% 1.00 [0.83, 1.21]
Subtotal (95% CI) 17.4% 0.92 [0.78, 1.08]
Heterogeneity: not significant (P = 0.20), I² = 40%
8.26.2 RCTs
Kamolratanakul (3) 82.6% 0.92 [0.87, 0.98]
0.7 0.85 1 1.2 1.5
Favours DOT Favours SAT
SAT vs DOT
48


Loss to follow up– RCTs
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Kamolratanakul 25.7% 2.00 [1.26, 3.16]
Malley 2001b 36.6% 1.11 [0.84, 1.46]
Zwarenstein 1998 (1) 20.6% 0.97 [0.57, 1.67]
Zwarenstein 2000 17.1% 1.22 [0.85, 2.28]
Total (95% CI) 100.0% 1.28 [0.93, 1.76]
0.2 0.5 1 2 5
Favours SAT Favours DOT
Heterogeneity: not significant (p=0.11), I² = 51%
SAT vs DOT
43


Loss to follow up– Obs
Risk Difference
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Akande 2010 (1) 6.2% 0.01 [-0.03, 0.02]
Akello 1999 5.4% 0.02 [-0.02, 0.06]
Alegre-Diaz 2014 5.6% 0.01 [-0.04, 0.06]
Aquinoshimakate 2008 6.0% 0.16 [0.14, 0.18]
Cavalcante 2007 (2) 6.0% -0.00 [-0.02, 0.01]
Cayla 2004 5.8% -0.05 [-0.09, -0.02]
Cayla 2009 6.1% -0.01 [-0.02, 0.00]
Daniel 2006 4.7% 0.07 [-0.01, 0.15]
Dye 2014 (3) 1.6% 0.22 [-0.02, 0.46]
Jasmer 2004 5.0% -0.03 [-0.10, 0.04]
Kapata 2009 5.2% 0.34 [0.27, 0.40]
Mathema 2003 (4) 5.2% 0.13 [0.08, 0.19]
Mingo 2005 4.3% -0.07 [-0.16, 0.01]
Okwera-ak 2007 (5) 6.0% -0.02 [-0.05, 0.01]
Ong-Golg 2001 4.6% 0.22 [0.13, 0.31]
Ormerod 2002 5.4% 0.00 [-0.06, 0.06]
Pungrassami 2002 (6) 3.5% 0.11 [-0.02, 0.23]
Padilla-Chavez 2007 (7) 4.5% 0.00 [-0.09, 0.09]
Szczesniak 2009 4.7% 0.15 [0.06, 0.23]
Tshokodo 2003 4.1% 0.02 [-0.08, 0.13]
Total (95% CI) 100.0% 0.06 [0.02, 0.09]
-0.5 -0.25 0 0.25 0.5
Favours SAT Favours DOT
Heterogeneity: significant (p<0.00001), I² = 95%
SAT vs DOT
44


Relapse - RCTs
Risk Ratio
Risk Ratio
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
TB Research Center 0.58 [0.31, 1.09]
0.5 0.7 1 1.5 2
Favours SAT Favours DOT
SAT vs DOT
45


Relapse – Obs
Risk Difference
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Balasubramanian 2000 (1) 15.0% 0.10 [0.00, 0.20]
Jasmer 2004 18.6% 0.02 [-0.01, 0.05]
Jean 2006 18.3% -0.00 [-0.04, 0.03]
Moz 1999 13.8% 0.08 [-0.05, 0.21]
Ormerod 2002 16.2% -0.04 [-0.12, 0.05]
Well 1994 18.1% 0.15 [0.11, 0.20]
Total (95% CI) 100.0% 0.06 [-0.03, 0.15]
-1 -0.5 0 0.5 1
Favours SAT Favours DOT
Heterogeneity: significant (p<0.00001), I² = 95%
SAT vs DOT
46


Adherence
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
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Subtotal (95% CI) 67.0% 0.83 [0.80, 0.86]
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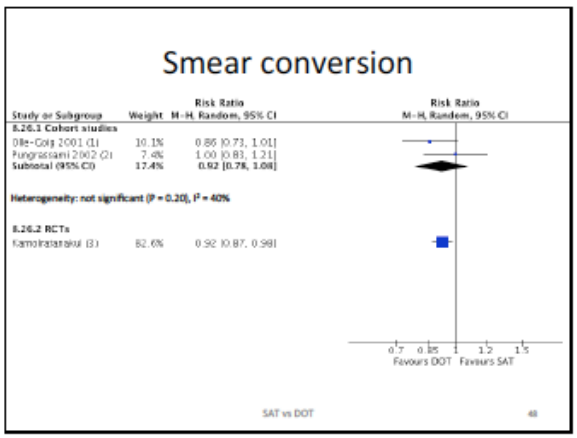
0.7 0.85 1 1.2 1.5
Favours DOT Favours SAT
SAT vs DOT
47


Smear conversion
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.26.1 Cohort studies
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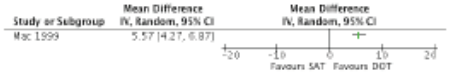
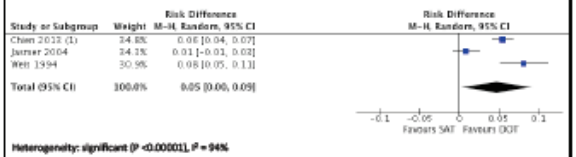
Pungrassami 2002 (2) 7.4% 1.00 [0.83, 1.21]
Subtotal (95% CI) 17.4% 0.92 [0.78, 1.08]
Heterogeneity: not significant (P = 0.20), I² = 40%
8.26.2 RCTs
Kamolratanakul (3) 82.6% 0.92 [0.87, 0.98]
0.7 0.85 1 1.2 1.5
Favours DOT Favours SAT
SAT vs DOT
48

Time to smear conversion



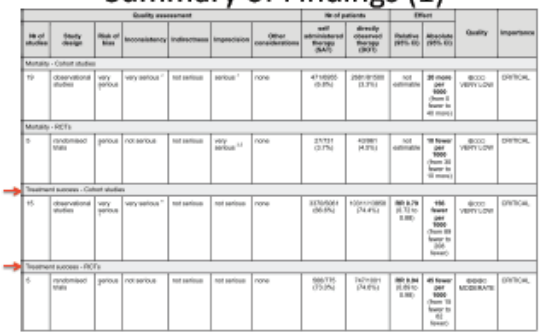
SAT vs DOT 49

Acquisition of drug resistance



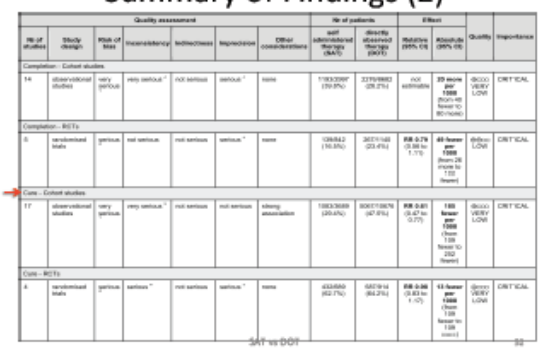
SAT vs DOT 50

Summary of Findings (1)



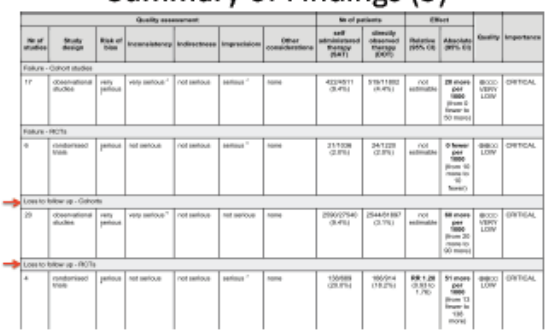
SAT vs DOT 51

Summary of Findings (2)



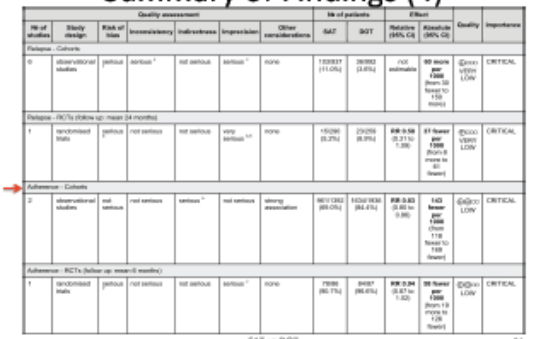
SAT vs DOT 52

Summary of Findings (3)



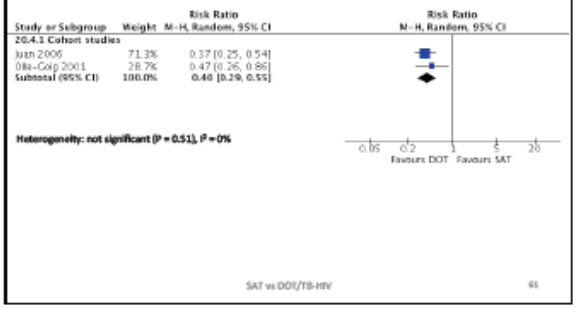
SAT vs DOT 53

Summary of Findings (4)

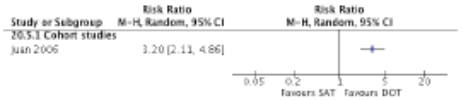


SAT vs DOT 54

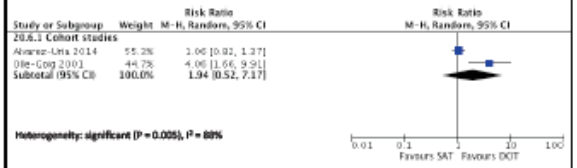
Cure



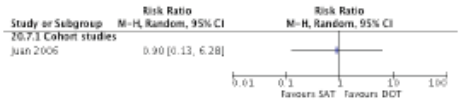
Failure



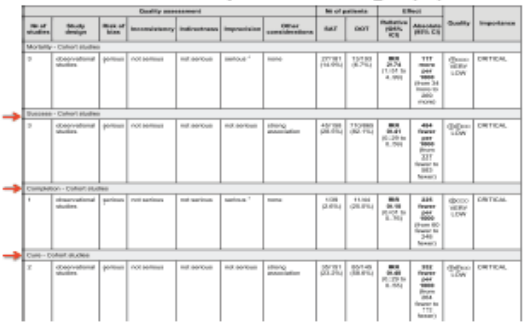
Loss to follow up



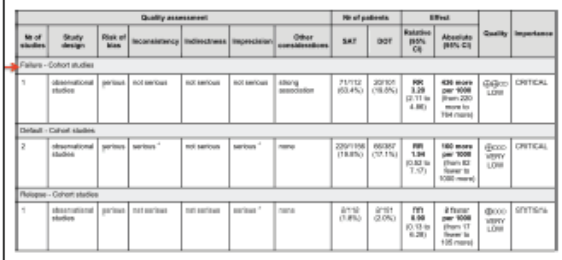
Relapse



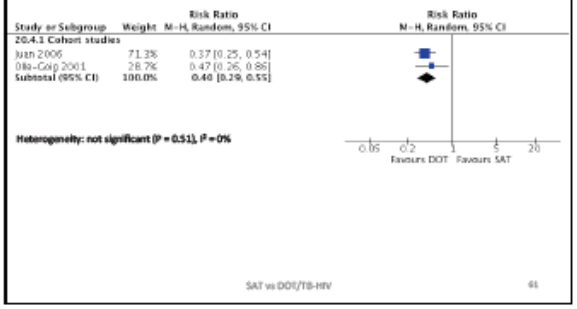
Summary of Findings (1)



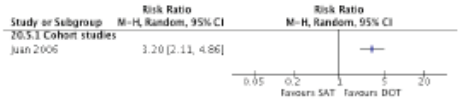
Summary of Findings (2)



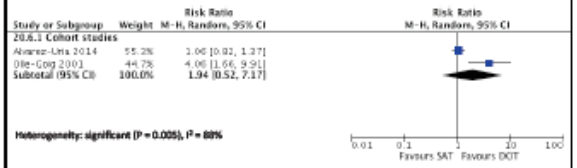
Cure



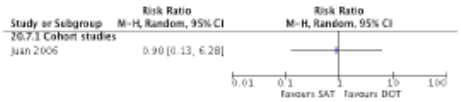
Failure



Loss to follow up



Relapse



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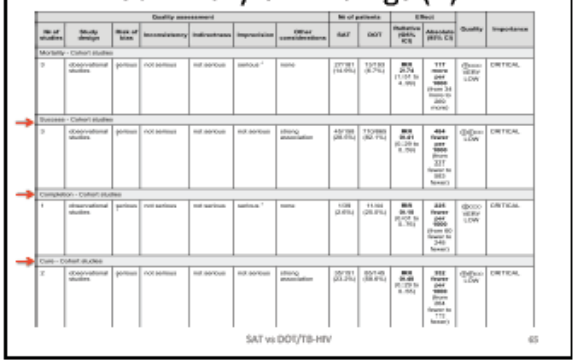
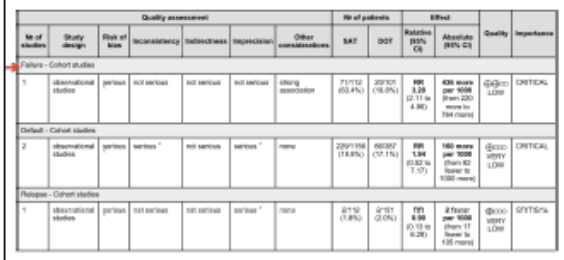


Summary of Findings (2)



Observational studies

Author	Year	Study design	Country	N	Condition	DOT administration
Xu	2009	Prospective	China	670	-PTB (smear +)	-DOT by family member, health worker, or village doctor
Tripathy	2013	Retrospective	India	1789	-New -PTB (smear +) -Adults & children	-DOT by community volunteers (CHWs, physicians, alternative medicine doctors, shopkeepers, teachers) vs institutional providers (TB health visitors, staff nurses, auxiliary nurse midlives)
Wilkinson	1997	Retrospective	South Africa	1000	-No info -High HIV prevalent setting	-Choice of HW, CHW, or volunteer lay people. No distinction provided between HW & CHW.

DOT Providers 73

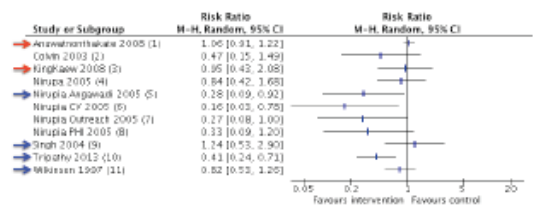
Quality – Obs

	Selection	Comparability	Outcome
Mathema	4	0	3
Aruwatmonthakate	4	0	3
Xu	4	2	3
Nirupa	3	0	0
Singh	4	0	1
Colvin	3	0	0
Kingkaew	4	2	1
Tripathy	4	0	2
Wilkinson	2	0	2

Newcastle Ottawa Scale

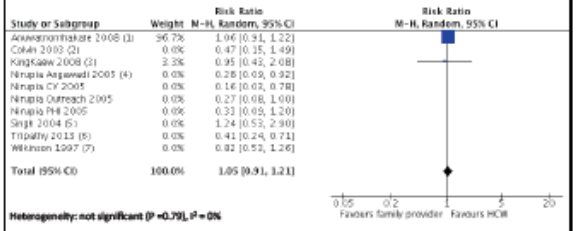
DOT Providers 74

Mortality



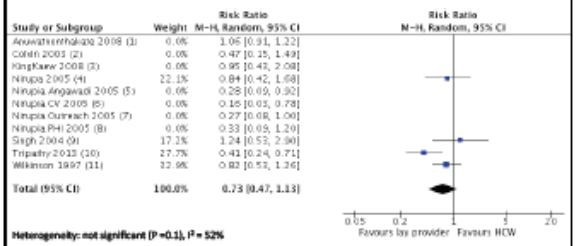
DOT Providers

Mortality



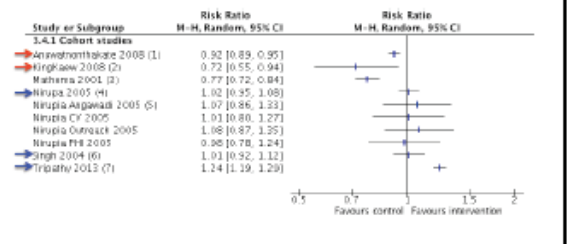
DOT Providers

Mortality



DOT Providers

Success



DOT Providers

Observational studies

Author	Year	Study design	Country	N	Condition	DOT administration
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DOT Providers 73

Quality – Obs

	Selection	Comparability	Outcome
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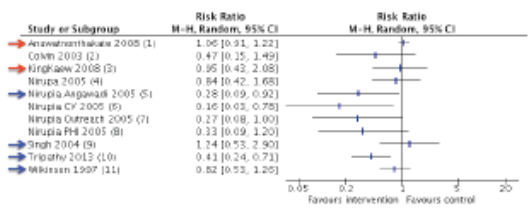
Anuwatmonthakate	4	0	3
Xu	4	2	3
Nirupa	3	0	0
Singh	4	0	1
Colvin	3	0	0
Kingkaew	4	2	1
Tripathy	4	0	2
Wilkinson	2	0	2

Newcastle Ottawa Scale

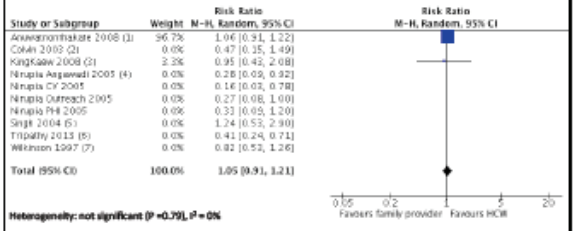
DOT Providers 74

Mortality



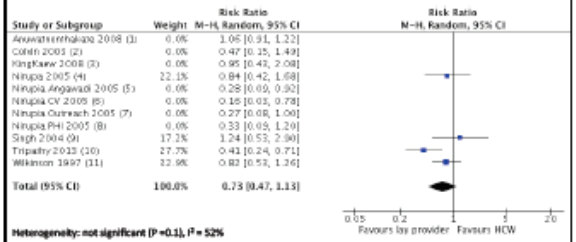
DOT Providers

Mortality



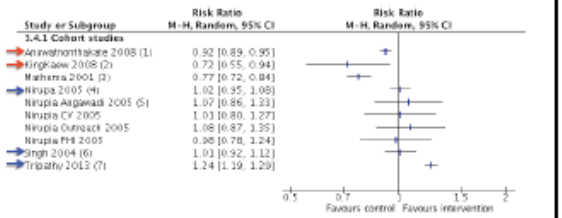
DOT Providers

Mortality

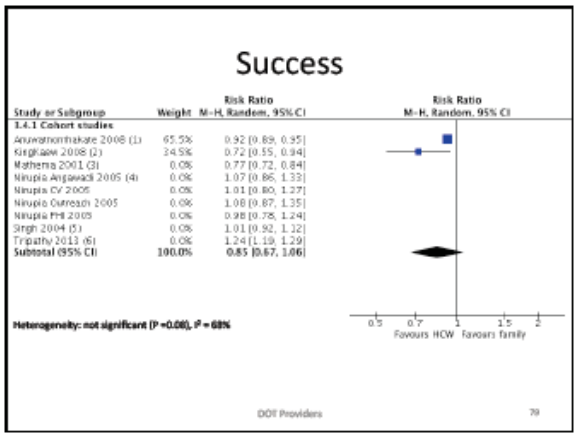


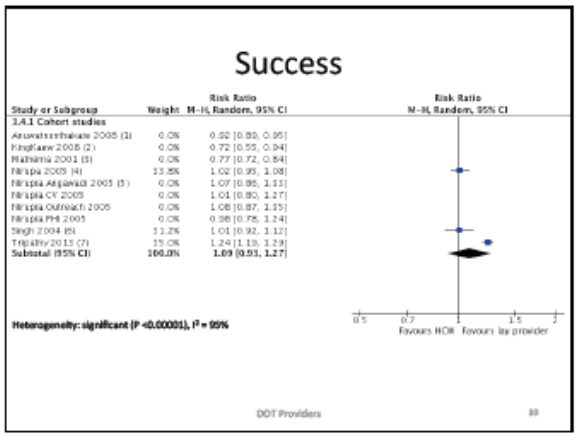
DOT Providers

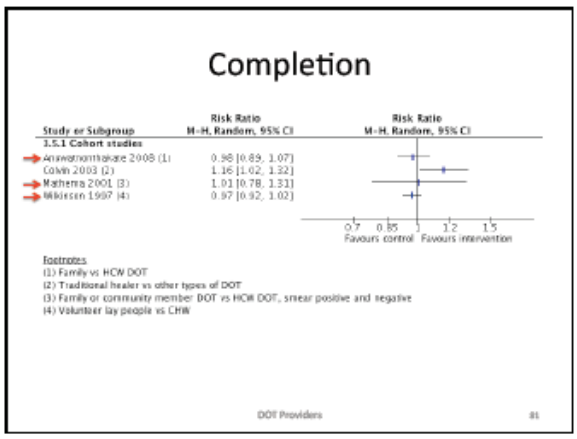
Success

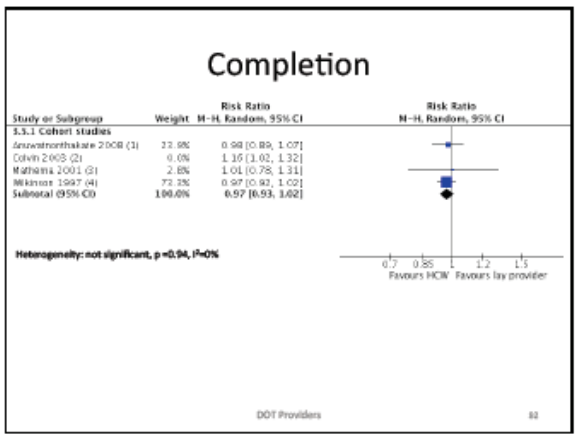


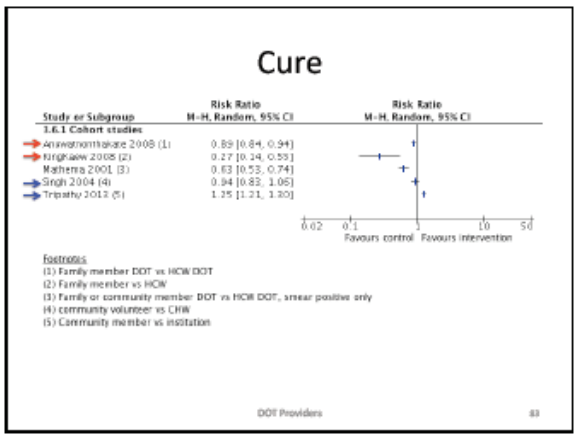
DOT Providers

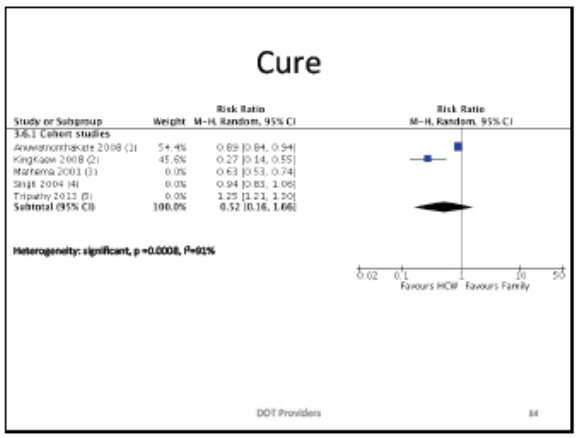

Success
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
3.4.1 Cohort studies
Anuwatnonthakate 2008 (1) 65.5% 0.92 [0.89, 0.95]
KingKaew 2008 (2) 34.5% 0.72 [0.55, 0.94]
Mathema 2001 (3) 0.0% 0.77 [0.72, 0.84]
Nirupia Angawadi 2005 (4) 0.0% 1.07 [0.86, 1.33]
Nirupia CV 2005 0.0% 1.01 [0.80, 1.27]
Nirupia Outreach 2005 0.0% 1.08 [0.87, 1.35]
Nirupia PHI 2005 0.0% 0.98 [0.78, 1.24]
Singh 2004 (5) 0.0% 1.01 [0.92, 1.12]
Tripathy 2013 (6) 0.0% 1.24 [1.19, 1.29]
Subtotal (95% CI) 100.0% 0.85 [0.67, 1.06]
Heterogeneity: not significant (P =0.08), I² = 68%
0.5 0.7 1 1.5 2
Favours HCW Favours family
DOT Providers
79


Success
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
3.4.1 Cohort studies
Anuwatnonthakate 2008 (1) 0.0% 0.92 [0.89, 0.95]
KingKaew 2008 (2) 0.0% 0.72 [0.55, 0.94]
Mathema 2001 (3) 0.0% 0.77 [0.72, 0.84]
Nirupia 2005 (4) 13.8% 1.02 [0.95, 1.08]
Nirupia Angawadi 2005 (5) 0.0% 1.07 [0.86, 1.33]
Nirupia CV 2005 0.0% 1.01 [0.80, 1.27]
Nirupia Outreach 2005 0.0% 1.08 [0.87, 1.35]
Nirupia PHI 2005 0.0% 0.98 [0.78, 1.24]
Singh 2004 (6) 11.2% 1.01 [0.92, 1.12]
Tripathy 2013 (7) 75.0% 1.24 [1.19, 1.29]
Subtotal (95% CI) 100.0% 1.09 [0.91, 1.27]
Heterogeneity: significant (P <0.00001), I² = 95%
0.5 0.7 1 1.5 2
Favours HCW Favours lay provider
DOT Providers
80

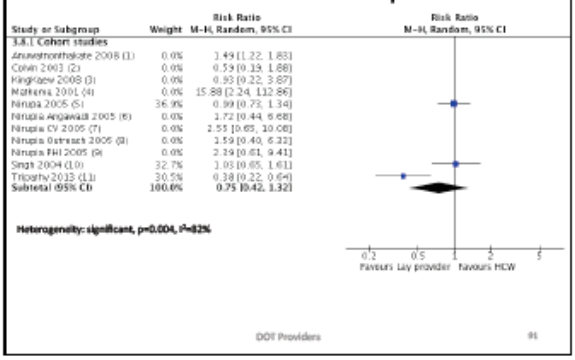

Completion
Risk Ratio
Risk Ratio
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
3.5.1 Cohort studies
Anuwatnonthakate 2008 (1) 0.98 [0.89, 1.07]
Colvin 2003 (2) 1.16 [1.02, 1.32]
Mathema 2001 (3) 1.01 [0.78, 1.31]
Wilkinson 1997 (4) 0.97 [0.92, 1.02]
0.7 0.85 1 1.2 1.5
Favours control Favours intervention
Footnotes
(1) Family vs HCW DOT
(2) Traditional healer vs other types of DOT
(3) Family or community member DOT vs HCW DOT, smear positive and negative
(4) Volunteer lay people vs CHW
DOT Providers
81


Completion
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
3.5.1 Cohort studies
Anuwatnonthakate 2008 (1) 72.9% 0.98 [0.89, 1.07]
Colvin 2003 (2) 0.0% 1.16 [1.02, 1.32]
Mathema 2001 (3) 2.8% 1.01 [0.78, 1.31]
Wilkinson 1997 (4) 72.1% 0.97 [0.92, 1.02]
Subtotal (95% CI) 100.0% 0.97 [0.93, 1.02]
Heterogeneity: not significant, p =0.94, I²=0%
0.7 0.85 1 1.2 1.5
Favours HCW Favours lay provider
DOT Providers
82

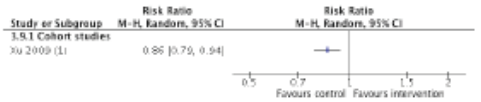

Cure
Risk Ratio
Risk Ratio
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
3.6.1 Cohort studies
Anuwatnonthakate 2008 (1) 0.89 [0.84, 0.94]
KingKaew 2008 (2) 0.27 [0.14, 0.53]
Mathema 2001 (3) 0.63 [0.53, 0.74]
Singh 2004 (4) 0.94 [0.83, 1.06]
Tripathy 2013 (5) 1.25 [1.21, 1.30]
0.02 0.1 1 10 50
Favours control Favours intervention
Footnotes
(1) Family member DOT vs HCW DOT
(2) Family member vs HCW
(3) Family or community member DOT vs HCW DOT, smear positive only
(4) community volunteer vs CHW
(5) Community member vs institution
DOT Providers
83


Cure
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
3.6.1 Cohort studies
Anuwatnonthakate 2008 (1) 54.4% 0.89 [0.84, 0.94]
KingKaew 2008 (2) 45.6% 0.27 [0.14, 0.53]
Mathema 2001 (3) 0.0% 0.63 [0.53, 0.74]
Singh 2004 (4) 0.0% 0.94 [0.83, 1.06]
Tripathy 2013 (5) 0.0% 1.25 [1.21, 1.30]
Subtotal (95% CI) 100.0% 0.52 [0.16, 1.66]
Heterogeneity: significant, p =0.0008, I²=91%
0.02 0.1 1 10 50
Favours HCW Favours Family
DOT Providers
84

Loss to follow up

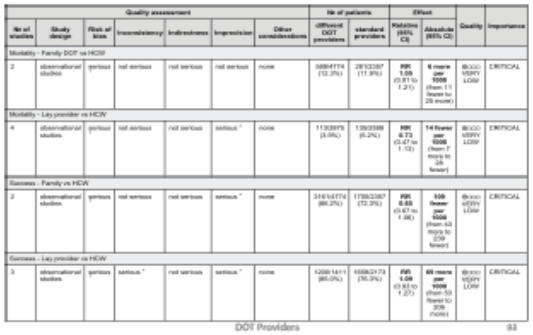


Adherence

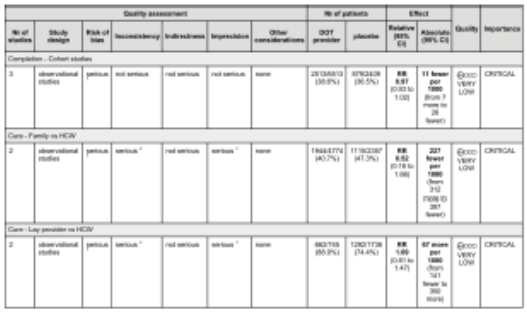


Footnotes:
(1) adherence as completing >90% of treatment doses, family member vs village doctor

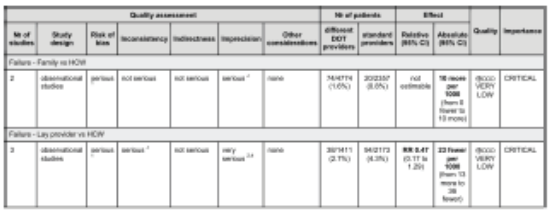
Summary of Findings (1)



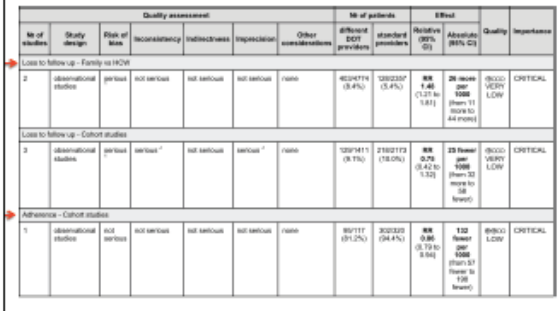
Summary of Findings (2)



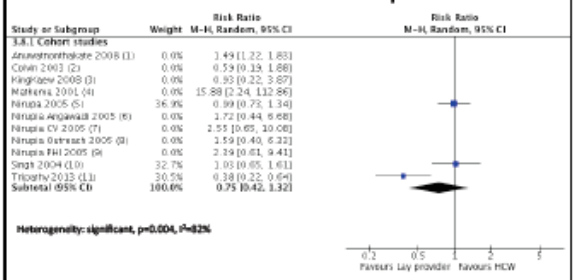
Summary of Findings (3)



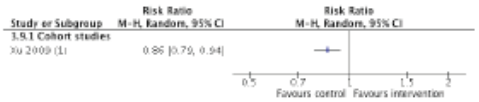
Summary of Findings (4)



Loss to follow up



Adherence



Footnotes:
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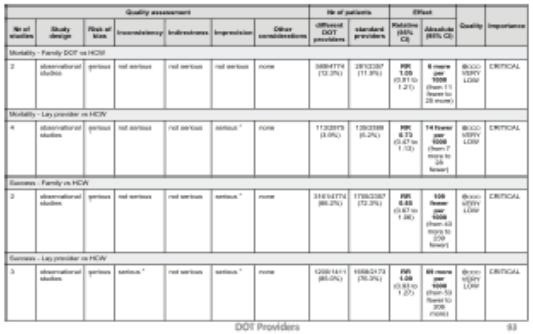
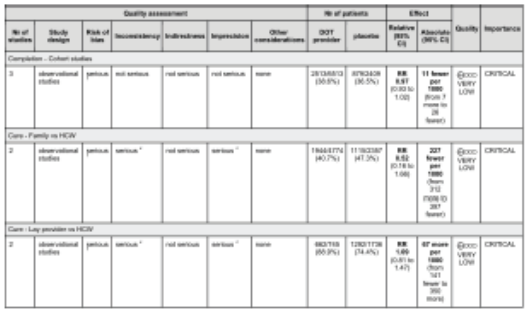
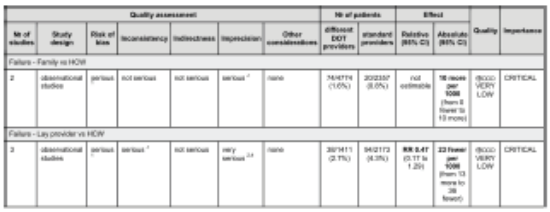
Summary of Findings (1)



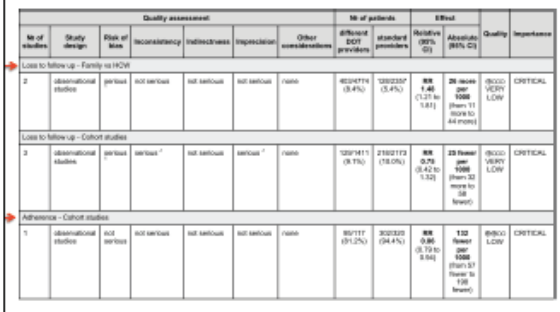
Summary of Findings (2)



Summary of Findings (3)



Summary of Findings (4)



Conclusion

- Similar performance of family or lay providers compared to institutional providers for most outcomes of interest.
- Higher rate of loss to follow up and lower rate of adherence with family DOT providers

DOT Providers 97

DOT location

98

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	DOT administration
Luelia	2003	RCT	Tanzania	522	-New -PTB (smear +)	-Community based vs institution based DOT
Wandwalo	2004	RCT	Tanzania	587	-Adults & children -New -PTB (smear +/-) -EPTB	-Community (family or former TB patient) vs health clinic DOT
Wright	2004	RCT	Swaziland	1353	-Adults & children -PTB (smear +/-) -EPTB -New & retreatment	-DOT by CHW (not at home) vs family member
Newell	2006	RCT	Nepal	907	-PTB (smear +) -≥15 years old -New	-Community based DOT vs family member DOT

DOT Location 99

Observational studies

Author	Year	Study design	Country	N	Condition	DOT administration
Akkslp	1999	Prospective	Thailand	779	-PTB (smear +)	DOT, family member or village volunteer
Banerjee	2000	Prospective	Malawi	600	-PTB (smear +/-) -EPTB -New	-DOT at home vs health center vs hospital
Becu-Bleumink	2001	Prospective	Indonesia	2353	-PTB (smear +) -New	-DOT in community vs clinic -6 times/week DOT by fam member during intensive phase, 5 times/fortnight during continuation phase
Cavalcante	2007	Retrospective	Brazil	1811	-PTB (smear +/-) -TB/HIV -EPTB	-DOT in community (home or church by CHW) vs clinic
Dobler	2015	Retrospective	Mongolia	2181	-PTB (smear +) -≥ 15 years old	-Daily DOT at home by volunteers -DOT at cafeterias -Clinic DOT
Dudley	2003	Prospective	South Africa	2873	-PTB -EPTB -≥ 15 years -New & retreatment	-Daily DOT at clinic or community (at CHW's home)

DOT Location 100

Observational studies

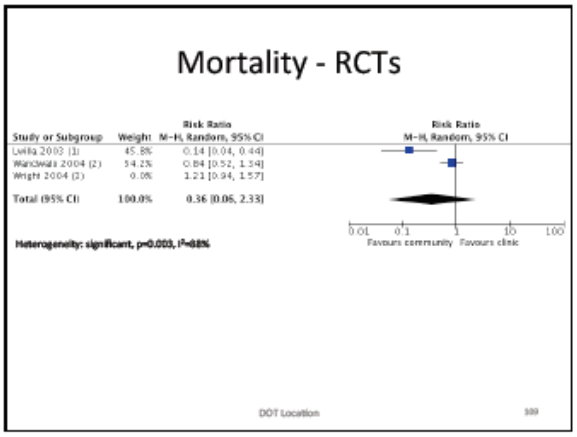
Author	Year	Study design	Country	N	Condition	DOT administration
Maciel	2010	Prospective	Brazil	171	-New -TB/HIV -PTB (smear +/-) -EPTB	-Daily DOT by a domiciliary supervisor at home or by CHW at clinic
Mfe	2003	Prospective	Zambia	168	-≥ 15 years -TB/HIV only -New -PTB (smear +)	-Daily DOT delivered at home + AIDS home care program -Daily DOT at clinic
Moalosi	2003	Retrospective	Botswana	633	-TB/HIV -PTB (smear +/-)	-Daily DOT by family at home -Clinic DOT
Niazi	2003	Prospective	Iraq	172	-New -PTB (smear +)	-Daily home vs clinic DOT
Wares	2001	Prospective	Nepal	327	-New & retreatment -PTB (smear +/-) -EPTB	-Daily DOT via health post, clinic, or hostel
Arora	2003	Prospective	India	2573	-Adults & children -PTB (smear +/-) -EPTB	-DOT by community member at patient's or member's house vs center based DOT

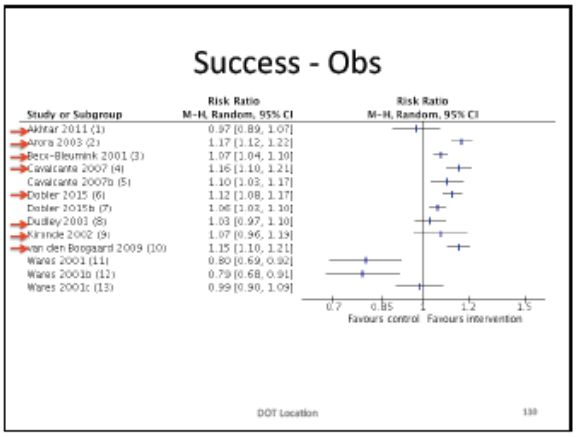
DOT Location 101

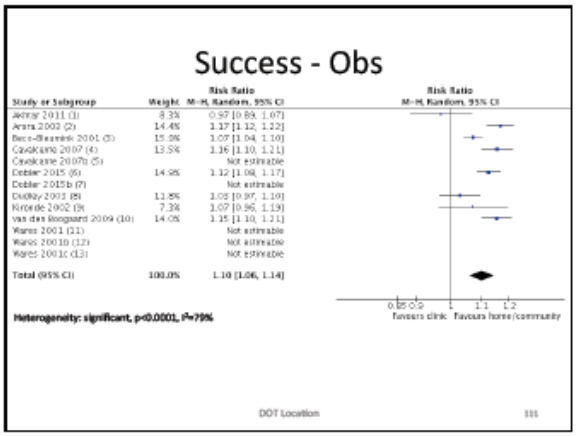
Observational studies

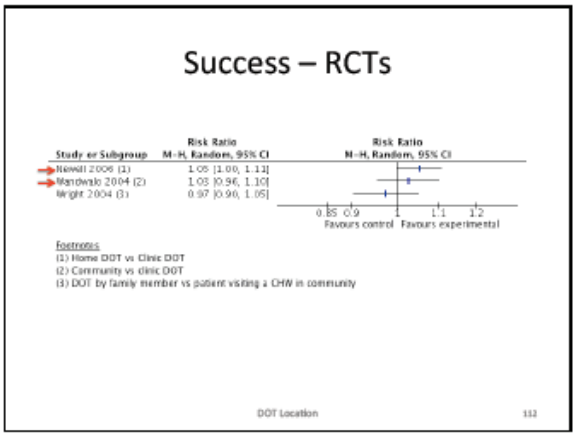
Author	Year	Study design	Country	N	Condition	DOT administration
Kironde	2002	Prospective	South Africa	505	-New & retreatment -≥ 15 years -PTB (smear +)	-Daily clinic or community-based DOT
Van den Boogaard	2009	Retrospective	Tanzania	2769	-Adults & children -New & retreatment -PTB (smear +/-) -EPTB -TB/HIV	-Daily community vs clinic DOT
Manders	2001	Prospective	Malawi	75	-≥ 18 years -PTB (smear +/-) -EPTB	-Guardian-based (family) DOT vs health-center based vs inpatient
Xu	2009	Prospective	China	670	-PTB (smear +)	-DOT by family member, health worker, or village doctor
Akhtar	2011	Prospective	Pakistan	582	-PTB (smear +) -≥15 years -New & retreatment -Excluded drug resistant	-Clinic DOT 3x/wk intensive phase, then 3x/wk continuation phase -Family DOT

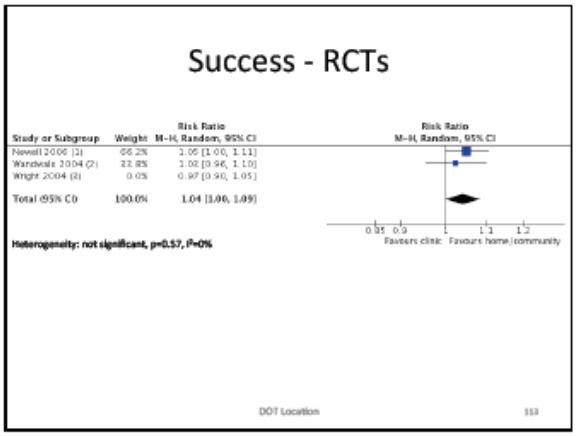
DOT Location 102

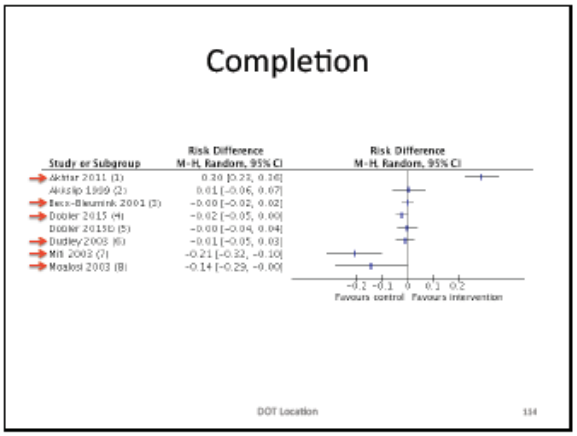

Mortality - RCTs
Study or Subgroup
Weight
Risk Ratio M-H, Random, 95% CI
Risk Ratio M-H, Random, 95% CI
Lwila 2003 (1) 45.8% 0.14 [0.04, 0.44]
Wandwalo 2004 (2) 54.2% 0.84 [0.52, 1.34]
Wright 2004 (3) 0.0% 1.21 [0.94, 1.57]
Total (95% CI) 100.0% 0.36 [0.06, 2.33]
Heterogeneity: significant, p=0.003, I²=88%
0.01 0.1 1 10 100
Favours community Favours clinic
DOT Location
109

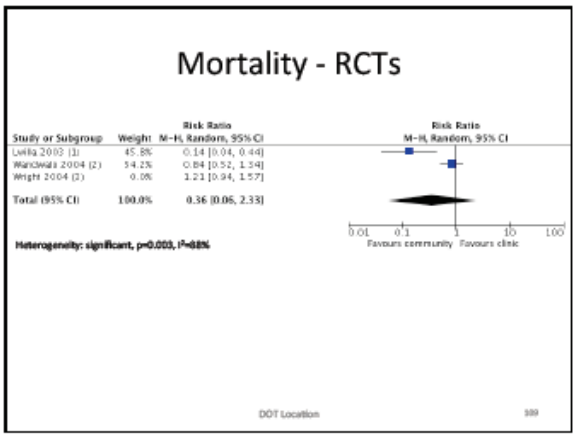

Success - Obs
Study or Subgroup
Risk Ratio M-H, Random, 95% CI
Risk Ratio M-H, Random, 95% CI
Akhtar 2011 (1) 0.97 [0.89, 1.07]
Arora 2003 (2) 1.17 [1.12, 1.22]
Beck-Bleumink 2001 (3) 1.07 [1.04, 1.10]
Cavalcante 2007 (4) 1.16 [1.10, 1.21]
Cavalcante 2007b (5) 1.10 [1.03, 1.17]
Dobler 2015 (6) 1.12 [1.08, 1.17]
Dobler 2015b (7) 1.06 [1.02, 1.10]
Dudley 2003 (8) 1.03 [0.97, 1.10]
Kirande 2002 (9) 1.07 [0.96, 1.19]
van den Boogaard 2009 (10) 1.15 [1.10, 1.21]
Wares 2001 (11) 0.80 [0.69, 0.92]
Wares 2001b (12) 0.79 [0.68, 0.91]
Wares 2001c (13) 0.99 [0.90, 1.09]
0.7 0.85 1 1.2 1.5
Favours control Favours intervention
DOT Location
110

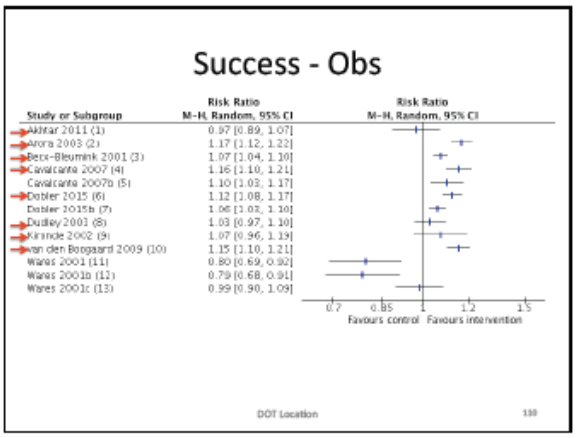

Success - Obs
Study or Subgroup
Weight
Risk Ratio M-H, Random, 95% CI
Risk Ratio M-H, Random, 95% CI
Akhtar 2011 (1) 8.3% 0.97 [0.89, 1.07]
Arora 2002 (2) 14.4% 1.17 [1.12, 1.22]
Beck-Bleumink 2001 (3) 15.0% 1.07 [1.04, 1.10]
Cavalcante 2007 (4) 13.5% 1.16 [1.10, 1.21]
Cavalcante 2007b (5) Not estimable
Dobler 2015 (6) 14.9% 1.12 [1.08, 1.17]
Dobler 2015b (7) Not estimable
Dudley 2003 (8) 13.8% 1.03 [0.97, 1.10]
Kirande 2002 (9) 7.3% 1.07 [0.96, 1.19]
van den Boogaard 2009 (10) 14.0% 1.15 [1.10, 1.21]
Wares 2001 (11) Not estimable
Wares 2001b (12) Not estimable
Wares 2001c (13) Not estimable
Total (95% CI) 100.0% 1.10 [1.06, 1.14]
Heterogeneity: significant, p<0.0001, I²=79%
0.85 0.9 1 1.1 1.2
Favours clinic Favours home/community
DOT Location
111

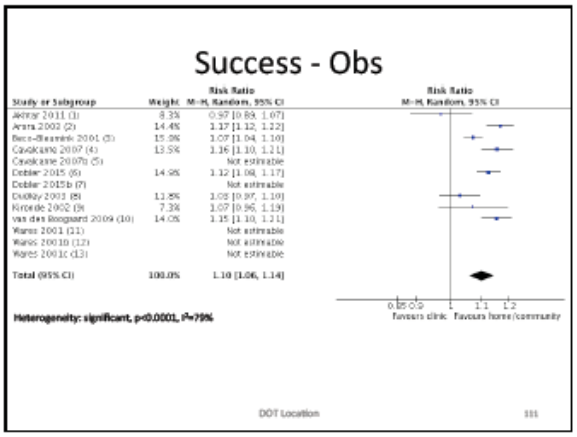

Success – RCTs
Study or Subgroup
Risk Ratio M-H, Random, 95% CI
Risk Ratio M-H, Random, 95% CI
Newell 2006 (1) 1.05 [1.00, 1.11]
Wandwalo 2004 (2) 1.03 [0.96, 1.10]
Wright 2004 (3) 0.97 [0.90, 1.05]
0.85 0.9 1 1.1 1.2
Favours control Favours experimental
Footnotes
(1) Home DOT vs Clinic DOT
(2) Community vs clinic DOT
(3) DOT by family member vs patient visiting a CHW in community
DOT Location
112

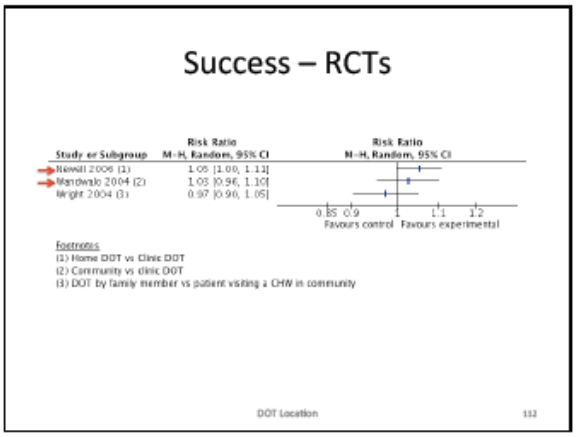

Success - RCTs
Study or Subgroup
Weight
Risk Ratio M-H, Random, 95% CI
Risk Ratio M-H, Random, 95% CI
Newell 2006 (1) 66.2% 1.05 [1.00, 1.11]
Wandwalo 2004 (2) 33.8% 1.02 [0.96, 1.10]
Wright 2004 (3) 0.0% 0.97 [0.90, 1.05]
Total (95% CI) 100.0% 1.04 [1.00, 1.09]
Heterogeneity: not significant, p=0.57, I²=0%
0.85 0.9 1 1.1 1.2
Favours clinic Favours home/community
DOT Location
113

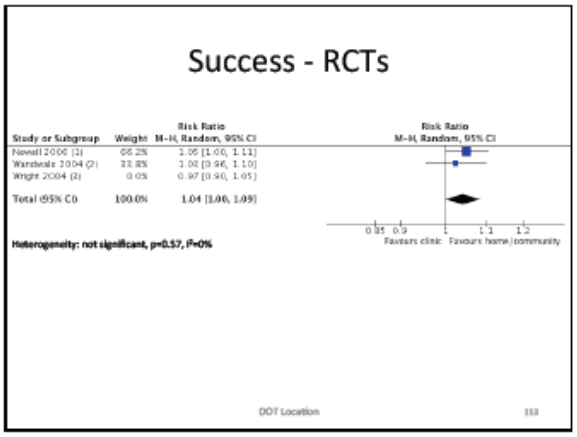

Completion
Study or Subgroup
Risk Difference M-H, Random, 95% CI
Risk Difference M-H, Random, 95% CI
Akhtar 2011 (1) 0.20 [0.22, 0.36]
Akkslp 1999 (2) 0.01 [-0.06, 0.07]
Beck-Bleumink 2001 (3) -0.00 [-0.02, 0.02]
Dobler 2015 (4) -0.02 [-0.05, 0.00]
Dobler 2015b (5) -0.00 [-0.04, 0.04]
Dudley 2003 (6) -0.01 [-0.05, 0.03]
Mit 2002 (7) -0.21 [-0.32, -0.10]
Moalosi 2003 (8) -0.14 [-0.29, -0.00]
-0.2 -0.1 0 0.1 0.2
Favours control Favours intervention
DOT Location
114

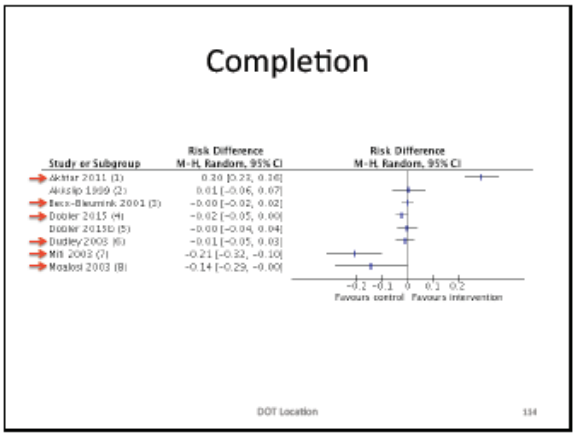

Mortality - RCTs
Risk Ratio
M-H, Random, 95% CI
Favours community
Favours clinic
DOT Location


Success - Obs
Risk Ratio
M-H, Random, 95% CI
Favours control
Favours intervention
DOT Location

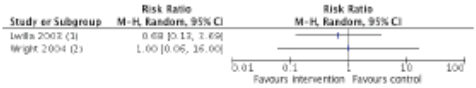

Success - Obs
Risk Ratio
M-H, Random, 95% CI
Favours clinic
Favours home/community
DOT Location


Success – RCTs
Risk Ratio
M-H, Random, 95% CI
Favours control
Favours experimental
DOT Location


Success - RCTs
Risk Ratio
M-H, Random, 95% CI
Favours clinic
Favours home/community
DOT Location

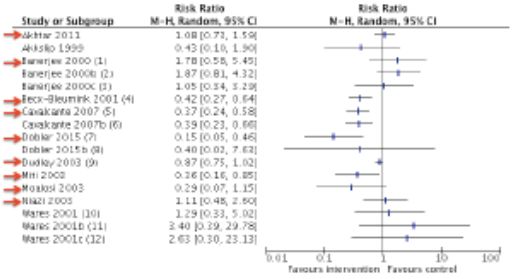

Completion
Risk Difference
M-H, Random, 95% CI
Favours control
Favours intervention
DOT Location

Failure – RCTs

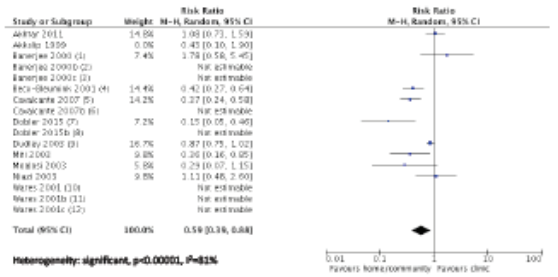


Footnotes
(1) Community vs clinic. Sig more people dropped out of CBDOT arm
(2) DOT by family member vs patient visiting a CHW in community

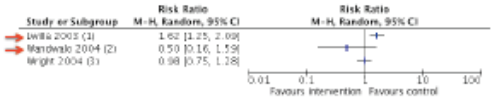
Loss to follow up – Obs



Loss to follow up – Obs

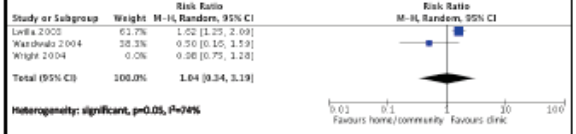


Loss to follow up – RCTs

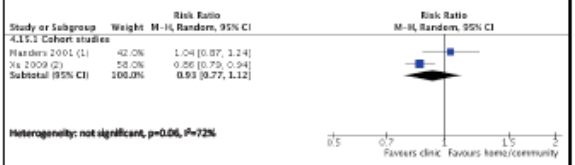


Footnotes
(1) Community vs Clinic
(2) Community vs Clinic
(3) Home vs community

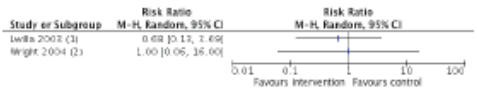
Loss to follow up – RCTs



Adherence

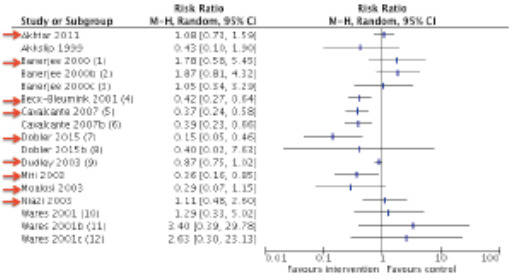


Failure – RCTs

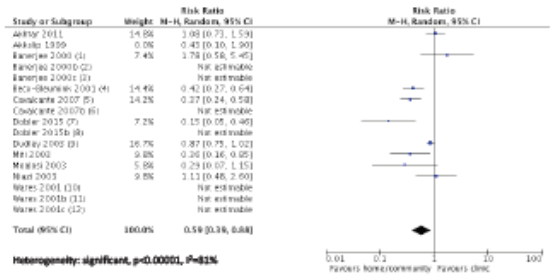


Footnotes
(1) Community vs clinic. Sig more people dropped out of CBDOT arm
(2) DOT by family member vs patient visiting a CHW in community

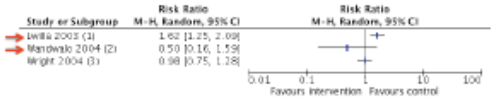
Loss to follow up – Obs



Loss to follow up – Obs

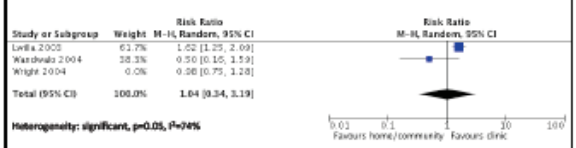


Loss to follow up – RCTs

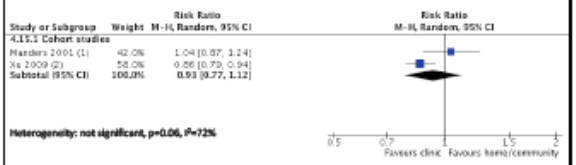


Footnotes
(1) Community vs Clinic
(2) Community vs Clinic
(3) Home vs community

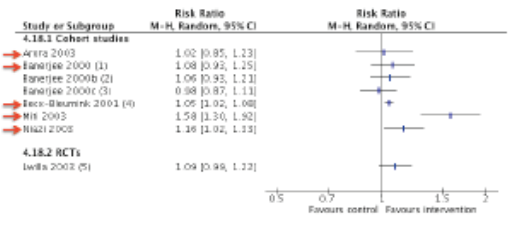
Loss to follow up – RCTs



Adherence

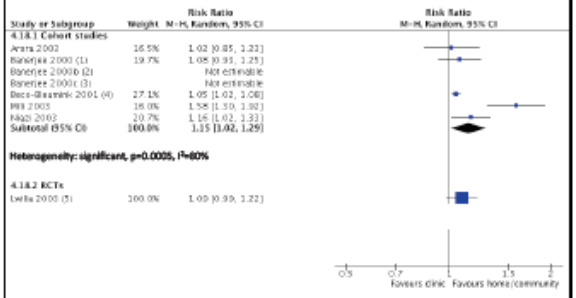


Sputum conversion rate



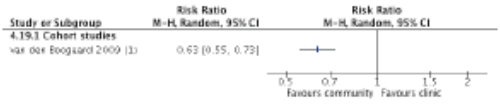
DOT Location 127

Sputum conversion rate



DOT Location 128

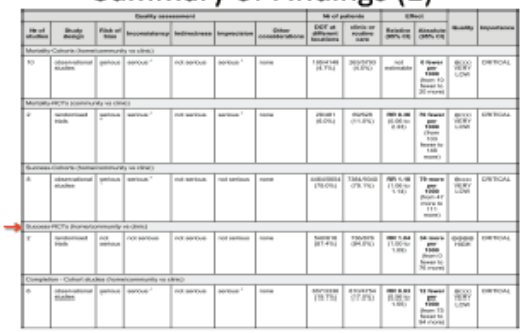
Unfavorable outcome



Footnotes
(1) Community based DOT vs facility based

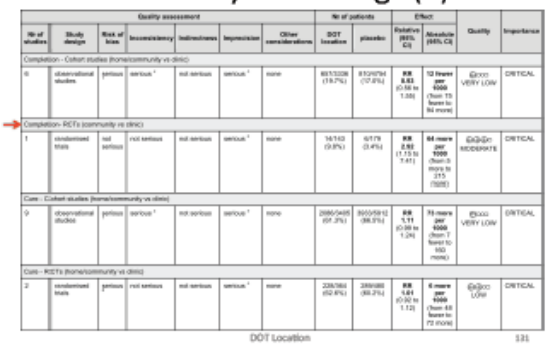
DOT Location 129

Summary of Findings (1)



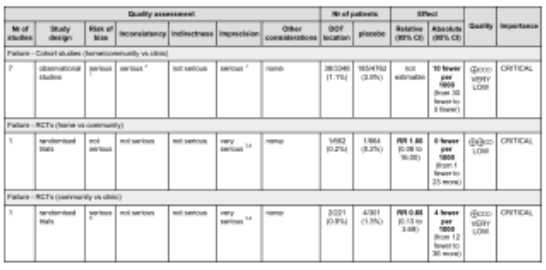
DOT Location 130

Summary of Findings (2)



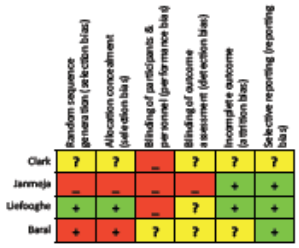
DOT Location 131

Summary of Findings (3)



DOT Location 132

Quality – RCTs



Cochrane risk of bias tool

Education & Counseling 139

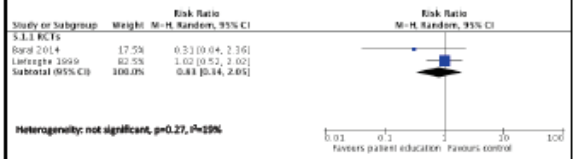
Quality – Obs

	Selection	Comparability	Outcome
Dick	4	2	3

Newcastle Ottawa Scale

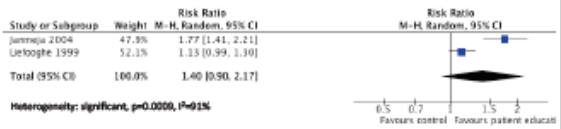
Education & Counseling 140

Mortality



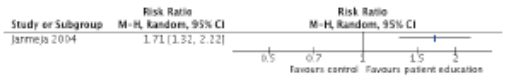
Education & Counseling 141

Treatment success



Education & Counseling 142

Treatment completion

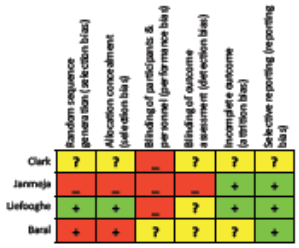


Education & Counseling 143

Cure

Education & Counseling 144

Quality – RCTs



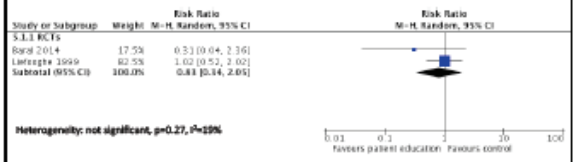
Cochrane risk of bias tool

Quality – Obs

	Selection	Comparability	Outcome
Dick	4	2	3

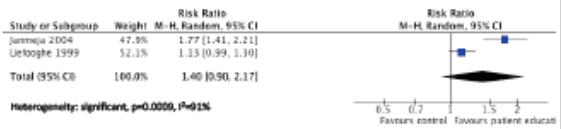
Newcastle Ottawa Scale

Mortality



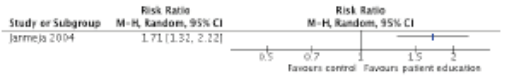
Heterogeneity: not significant, p=0.27, I²=19%

Treatment success



Heterogeneity: significant, p=0.0009, I²=91%

Treatment completion

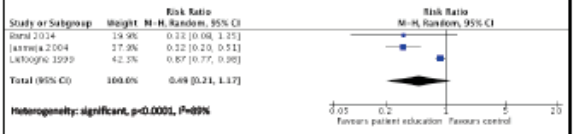


Cure

Failure

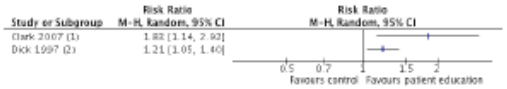
Education & Counseling 145

Loss to follow up



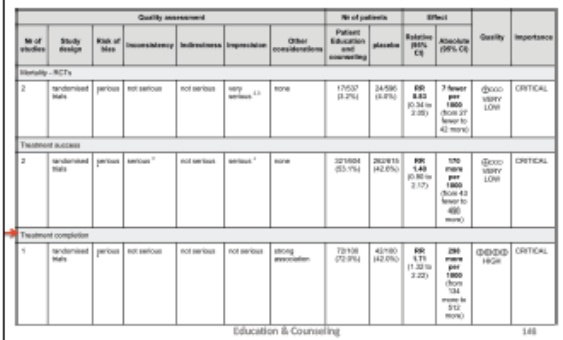
Education & Counseling 146

Adherence



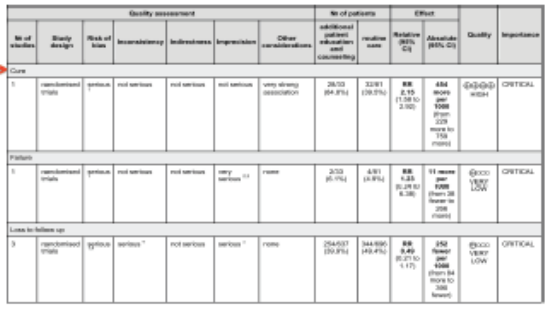
Education & Counseling 147

Summary of Findings (1)



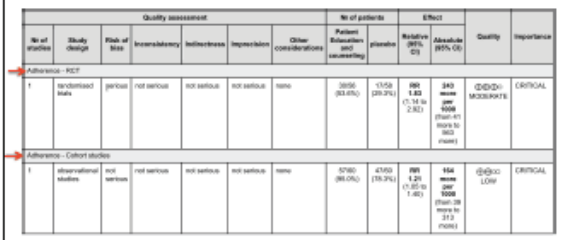
Education & Counseling 148

Summary of Findings (2)



Education & Counseling 149

Summary of Findings (3)



Education & Counseling 150

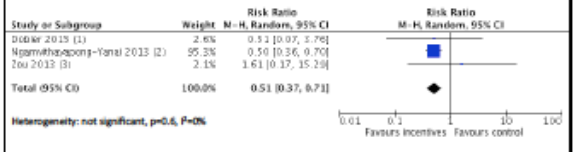
Quality – Obs

	Selection	Comparability	Outcome
Dobler	4	0	2
N-Yanai	1	0	3
Zou	3	0	3
Lu	3	1	2
Wei	1	0	3
Cantalice	3	0	3
Sripad	3	0	1
Tsai	2	2	3
Bock	3	0	2

Newcastle Ottawa Scale

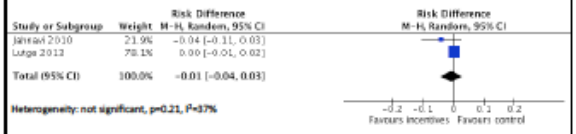
Incentives & Enablers 157

Mortality – Obs



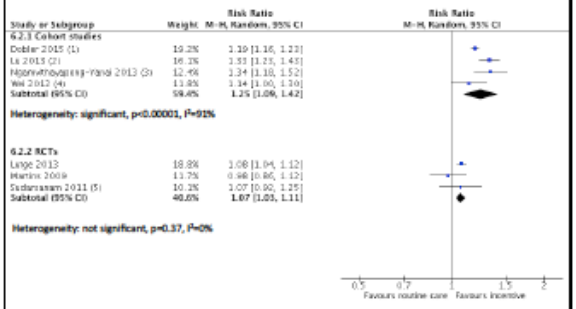
Incentives & Enablers 158

Mortality – RCTs



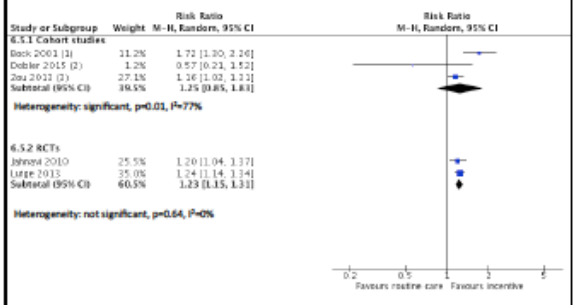
Incentives & Enablers 159

Success



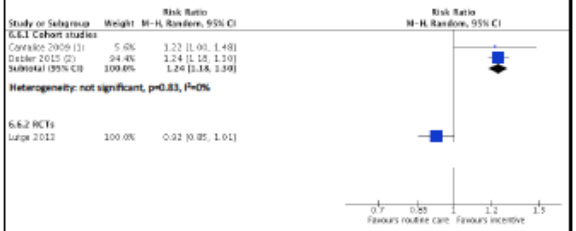
Incentives & Enablers 160

Completion



Incentives & Enablers 161

Cure



Incentives & Enablers 162

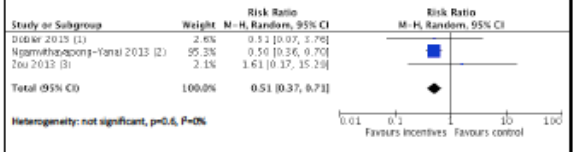
Quality – Obs

	Selection	Comparability	Outcome
Dobler	4	0	2
N-Yanai	1	0	3
Zou	3	0	3
Lu	3	1	2
Wei	1	0	3
Cantalice	3	0	3
Sripad	3	0	1
Tsai	2	2	3
Bock	3	0	2

Newcastle Ottawa Scale

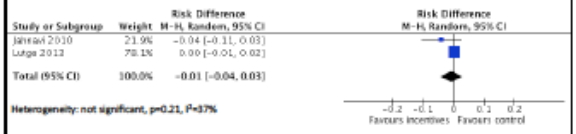
Incentives & Enablers 157

Mortality – Obs



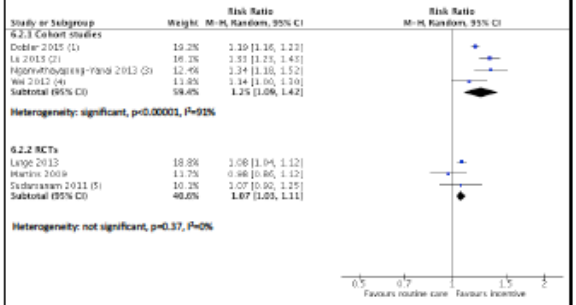
Incentives & Enablers 158

Mortality – RCTs



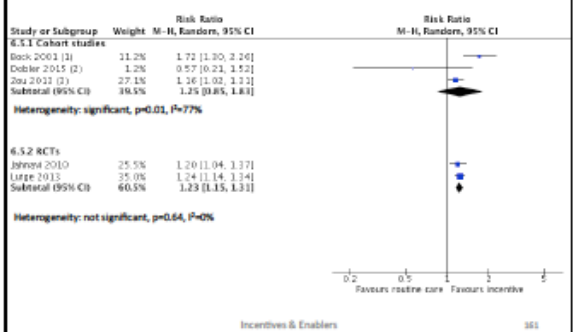
Incentives & Enablers 159

Success



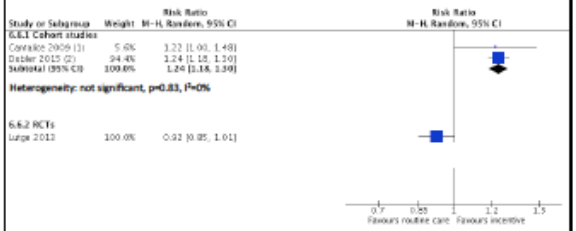
Incentives & Enablers 160

Completion



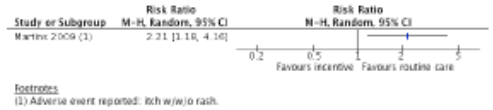
Incentives & Enablers 161

Cure



Incentives & Enablers 162

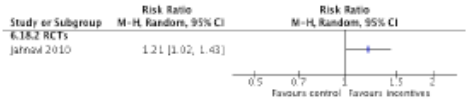
Adverse events



Footnotes
(1) Adverse event reported: itch w/w/o rash.

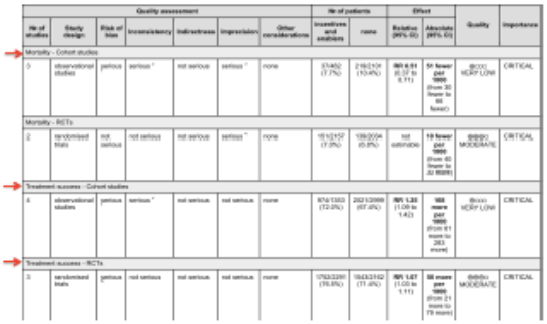
Incentives & Enablers 169

Sputum conversion rate



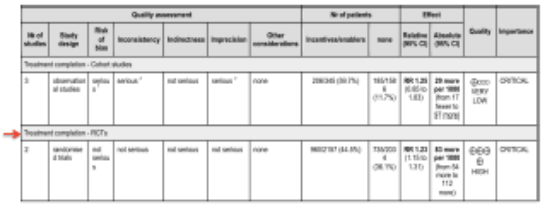
Incentives & Enablers 170

Summary of Findings (1)



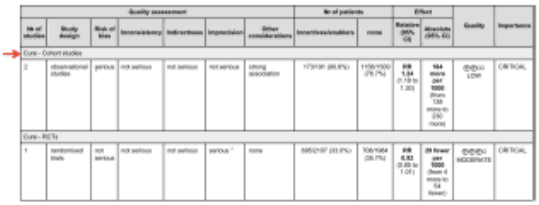
Incentives & Enablers 171

Summary of Findings (2)



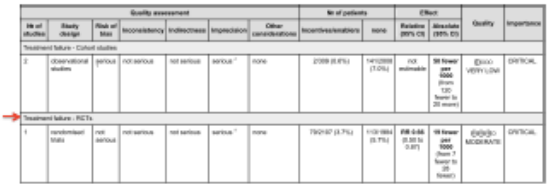
Incentives & Enablers 172

Summary of Findings (3)



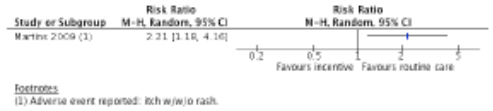
Incentives & Enablers 173

Summary of Findings (4)



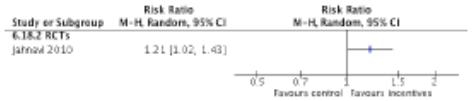
Incentives & Enablers 174

Adverse events

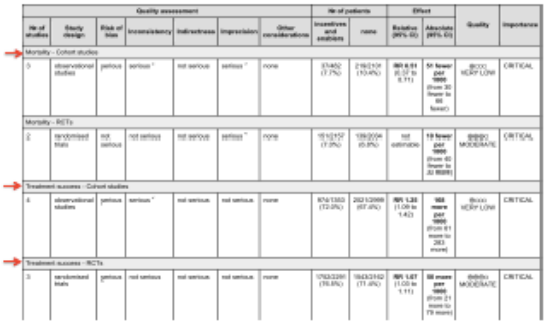


Footnotes
(1) Adverse event reported: itch w/w/o rash.

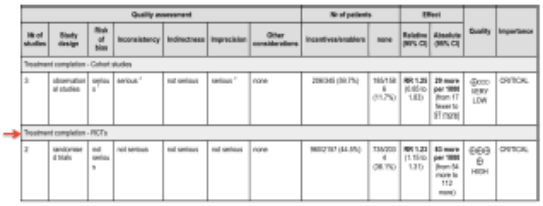
Sputum conversion rate



Summary of Findings (1)



Summary of Findings (2)



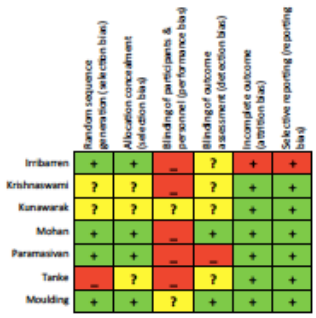
Summary of Findings (3)

Summary of Findings (4)

Observational studies

Author	Year	Study design	Country	# of patients	Condition	Intervention
Bronner	2012	Retrospective	South Africa	405673	-PTB (smear +) -New & retreatment -TB/HIV -MDR/TB	-CHWs traced patients who interrupted treatment
Sridal	2015	Prospective	Uganda	142	≥ 18 years -PTB (smear +/-) -New & retreatment -TB/HIV -EPTB	-Computer system to ensure CHWs see all patients and keep visit logs
Thomson	2011	Retrospective	Kenya	1169	-TB/HIV (100%) -PTB -Adults & children	-Social worker traced people who missed scheduled clinic appointments
Al-Hajjaj	2000	Retrospective	Saudi Arabia	628	-New & retreatment -PTB -EPTB	-Phone call, then home visit for missed appointments

Quality – RCTs



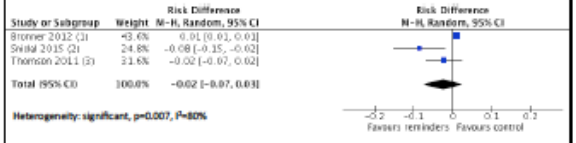
Cochrane risk of bias tool

Quality – Obs

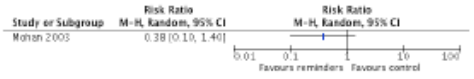
	Selection	Comparability	Outcome
Bronner	4	2	3
Sridal	4	1	3
Thomson	4	0	3
Al-Hajjaj	4	2	1

Newcastle Ottawa Scale

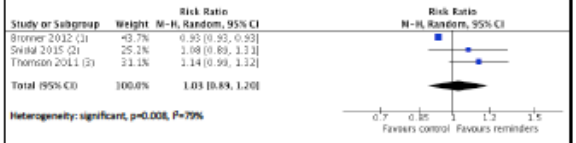
Mortality – Obs



Mortality – RCTs



Success – Obs



Observational studies

Author	Year	Study design	Country	# of patients	Condition	Intervention
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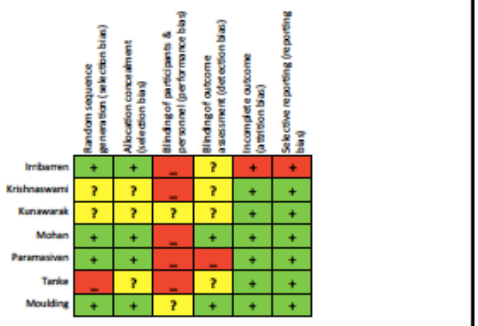
Sridal	2015	Prospective	Uganda	142	-≥ 18 years -PTB (smear +/-) -New & retreatment -TB/HIV -EPTB	-Computer system to ensure CHWs see all patients and keep visit logs
Thomson	2011	Retrospective	Kenya	1169	-TB/HIV (100%) -PTB -Adults & children	-Social worker traced people who missed scheduled clinic appointments
Al-Hajjaj	2000	Retrospective	Saudi Arabia	628	-New & retreatment -PTB -EPTB	-Phone call, then home visit for missed appointments

Reminders & Tracers 181

Quality – RCTs



Cochrane risk of bias tool

Reminders & Tracers 182

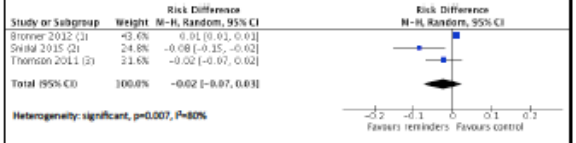
Quality – Obs

	Selection	Comparability	Outcome
Bronner	4	2	3
Sridal	4	1	3
Thomson	4	0	3
Al-Hajjaj	4	2	1

Newcastle Ottawa Scale

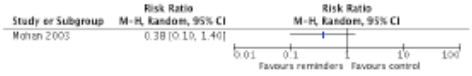
Reminders & Tracers 183

Mortality – Obs



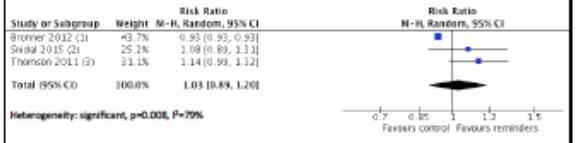
Reminders & Tracers 184

Mortality – RCTs

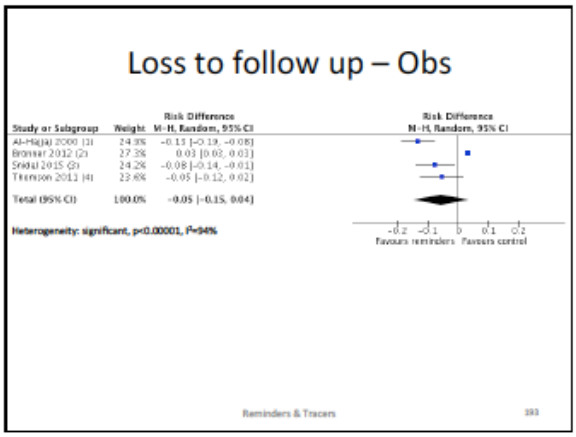


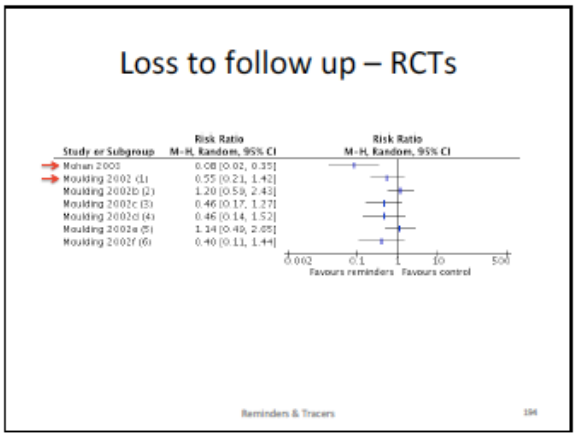
Reminders & Tracers 185

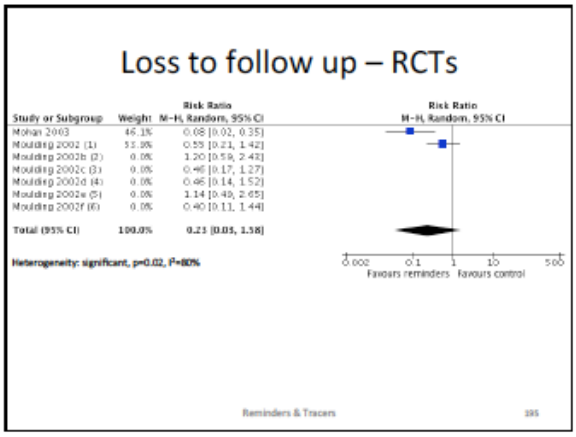
Success – Obs

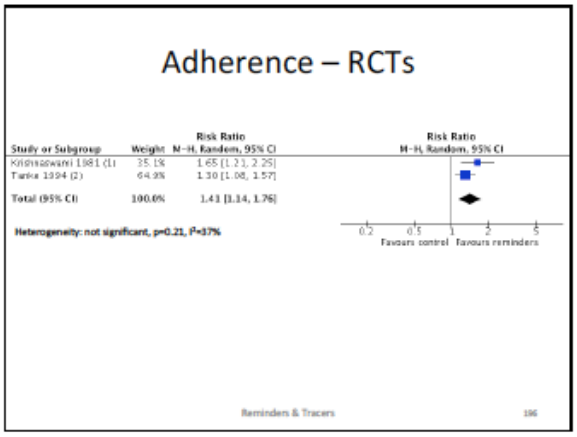


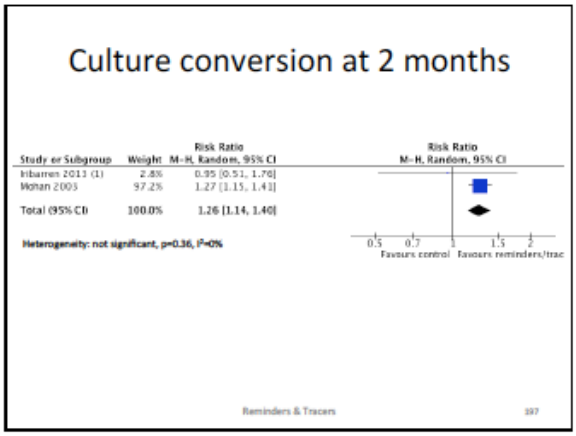
Reminders & Tracers 186

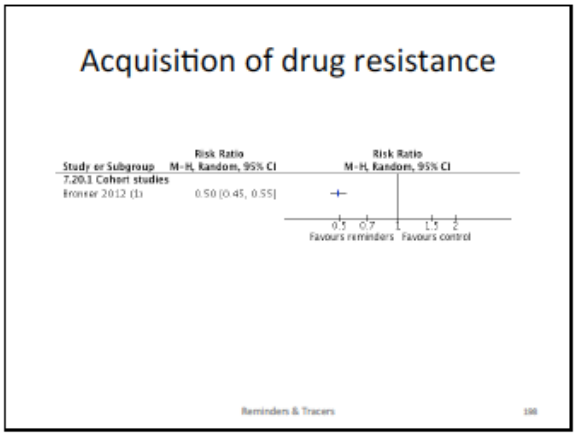

Loss to follow up – Obs
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
Al-Hajj 2000 (3) 24.9% -0.13 [-0.19, -0.08]
Bronner 2012 (2) 27.2% 0.03 [0.02, 0.03]
Sridal 2015 (2) 24.2% -0.08 [-0.14, -0.01]
Thomson 2013 (4) 23.8% -0.05 [-0.12, 0.02]
Total (95% CI) 100.0% -0.05 [-0.15, 0.04]
Heterogeneity: significant, p<0.00001, I²=94%
Risk Difference
M-H, Random, 95% CI
-0.2 -0.1 0 0.1 0.2
Favours reminders Favours control
Reminders & Tracers


Loss to follow up – RCTs
Risk Ratio
Study or Subgroup M-H, Random, 95% CI
Mohan 2003 0.08 [0.02, 0.35]
Moulding 2002 (1) 0.55 [0.21, 1.42]
Moulding 2002b (2) 1.20 [0.59, 2.43]
Moulding 2002c (3) 0.46 [0.17, 1.27]
Moulding 2002d (4) 0.46 [0.14, 1.52]
Moulding 2002e (5) 1.14 [0.49, 2.65]
Moulding 2002f (6) 0.40 [0.11, 1.44]
Risk Ratio
M-H, Random, 95% CI
0.002 0.1 1 10 500
Favours reminders Favours control
Reminders & Tracers

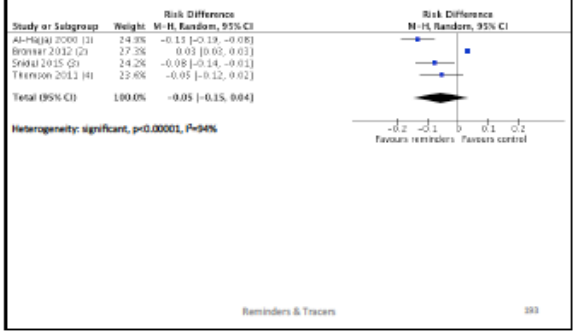

Loss to follow up – RCTs
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Mohan 2003 46.1% 0.08 [0.02, 0.35]
Moulding 2002 (1) 53.9% 0.55 [0.21, 1.42]
Moulding 2002b (2) 0.0% 1.20 [0.59, 2.43]
Moulding 2002c (3) 0.0% 0.46 [0.17, 1.27]
Moulding 2002d (4) 0.0% 0.46 [0.14, 1.52]
Moulding 2002e (5) 0.0% 1.14 [0.49, 2.65]
Moulding 2002f (6) 0.0% 0.40 [0.11, 1.44]
Total (95% CI) 100.0% 0.23 [0.03, 1.58]
Heterogeneity: significant, p=0.02, I²=80%
Risk Ratio
M-H, Random, 95% CI
0.002 0.1 1 10 500
Favours reminders Favours control
Reminders & Tracers


Adherence – RCTs
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Krishnaswami 1981 (1) 35.1% 1.65 [1.21, 2.25]
Tunkel 1994 (2) 64.9% 1.30 [1.08, 1.57]
Total (95% CI) 100.0% 1.43 [1.14, 1.76]
Heterogeneity: not significant, p=0.21, I²=37%
Risk Ratio
M-H, Random, 95% CI
0.2 0.5 1 2 5
Favours control Favours reminders
Reminders & Tracers

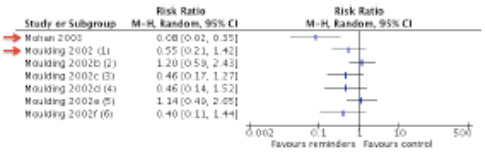

Culture conversion at 2 months
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Ribarren 2013 (1) 2.8% 0.95 [0.51, 1.76]
Mohan 2003 97.2% 1.27 [1.15, 1.41]
Total (95% CI) 100.0% 1.26 [1.14, 1.40]
Heterogeneity: not significant, p=0.36, I²=0%
Risk Ratio
M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours control Favours reminders/trac
Reminders & Tracers


Acquisition of drug resistance
Risk Ratio
Study or Subgroup M-H, Random, 95% CI
7.20.1 Cohort studies
Bronner 2012 (1) 0.50 [0.45, 0.55]
Risk Ratio
M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours reminders Favours control
Reminders & Tracers

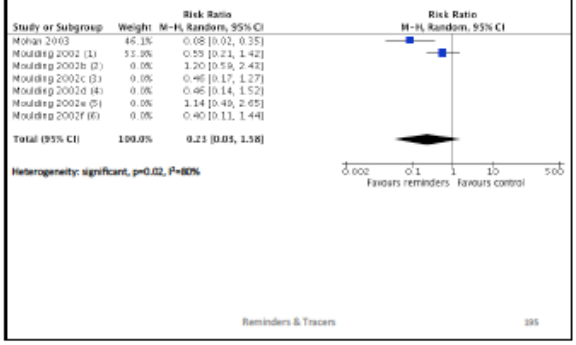
Loss to follow up – Obs



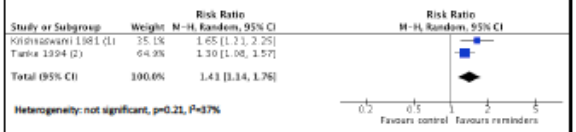
Loss to follow up – RCTs



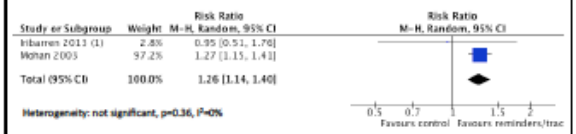
Loss to follow up – RCTs



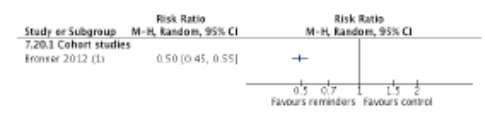
Adherence – RCTs



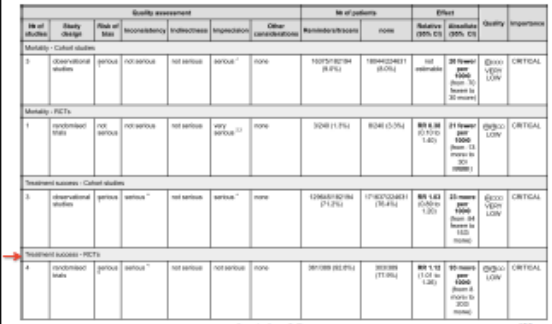
Culture conversion at 2 months



Acquisition of drug resistance

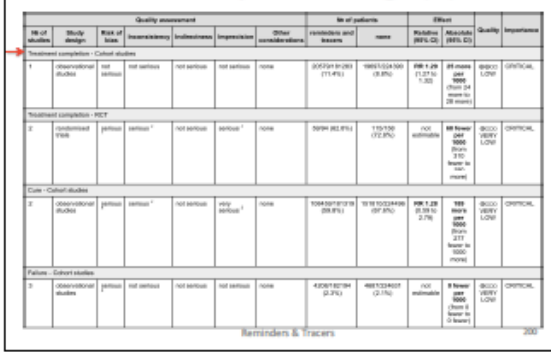


Summary of Findings (1)



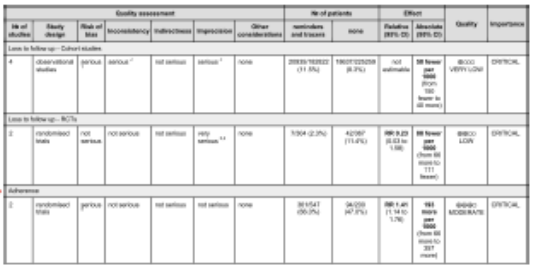
Reminders & Tracers 199

Summary of Findings (2)



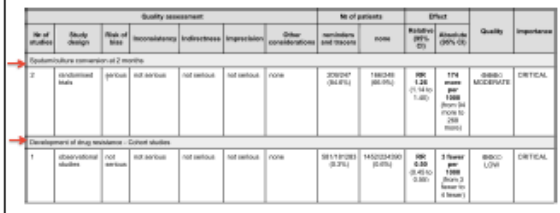
Reminders & Tracers 200

Summary of Findings (3)



Reminders & Tracers 201

Summary of Findings (4)



Reminders & Tracers 202

Conclusion

- Higher rate of treatment success, completion, adherence, and sputum conversion with reminders/tracers
- Lower rate of drug resistance development with reminders/tracers

Reminders & Tracers 203

Mixed interventions

204

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Population	Intervention
Khortwong	2013	Quasi-RCT	Thailand	100	-Undocumented migrant -New TB cases ->70% smear positive	-DOT + patient education and monthly home visits vs DOT alone
Morisky	1990	RCT	USA	88	-New -≥ 18 years	-Health education and $10 voucher at each monthly visit and $40 if no missed treatment vs monthly clinic follow up alone
Baral	2014	RCT	Nepal	156	-MDR-TB -Adults	-Counseling + financial incentive ($28/mo) q2-3 wks vs none
Drabo	2009	RCT	Burkina Faso	333	-PTB (smear +)	-Food + home visit +psychosocial support vs SAT
Thiam	2007	RCT	Senegal	1522	-Adults -PTB (smear +) -New	-Counseling, choice of DOT supporter, and reinforcement activities vs clinic based DOT
Hsieh	2008	RCT	Taiwan	96	-≥ 18 years -Excluded EPTB	-DOT in intensive phase, home visit continuation phase and health education -Control: initial ward care followed by monthly clinic follow up

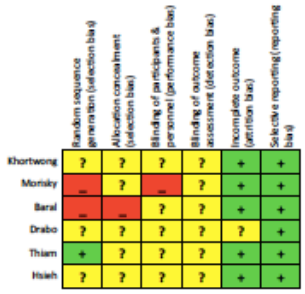
Observational studies

Author	Year	Study design	Country	# of patients	Condition	Intervention
Atkins	2011	Prospective	South Africa	5833	-≥ 18 years old -PTB (smear +/-) -EPTB -New & retreatment -TB/HIV (>50%) -Excluded M/XDR-TB	-Enhanced DOT with staff training, treatment supporters, and counseling vs standard DOT
Farmer	1991	Prospective	Haiti	60	-PTB -EPTB -TB/HIV	-Daily home visits, monthly reminder visits, food, financial incentive vs SAT
Jasmer	2004	Retrospective	USA	372	-PTB (culture +) -Excluded EPTB -TB/HIV -Adults & children	-DOT + incentives/enablers at home, clinic, or workplace vs SAT
Soares	2013	Prospective	Brazil	2623	-Adults & children -PTB (smear +/-) -EPTB -New & retreatment -TB/HIV	-DOT + psychosocial intervention + counseling and education + food incentives vs SAT
Yassin	2013	Prospective	Ethiopia	5090	-PTB (smear +/-) -EPTB -Adults & children	-Hospital capacity strengthening, staff education, mobile phone for HCWs, home-based DOT vs clinic/ community based DOT

Observational studies

Author	Year	Study design	Country	# of patients	Condition	Intervention
Chan	2013	Retrospective	Taiwan	390	-MDR-TB (100%) -PTB -New & retreatment -Adults	-Home DOT + incentives/ enablers, optional inpatient component vs hospital and then clinic DOT.
Garden	2012	Prospective	Russia	518	-Adults -New & retreatment (77%) -PTB (smear +/-)	-DOT + food incentive, psychosocial support vs SAT
Davidson	1998	Retrospective	USA	319	-Adults & children -TB/HIV -EPTB -PTB -MDR-TB	-Clinic or home DOT, 5 x/wk, intensive phase, included food coupons, bus tokens vs SAT

Quality – RCTs



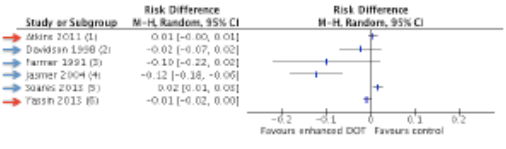
Cochrane risk of bias tool

Quality – Obs

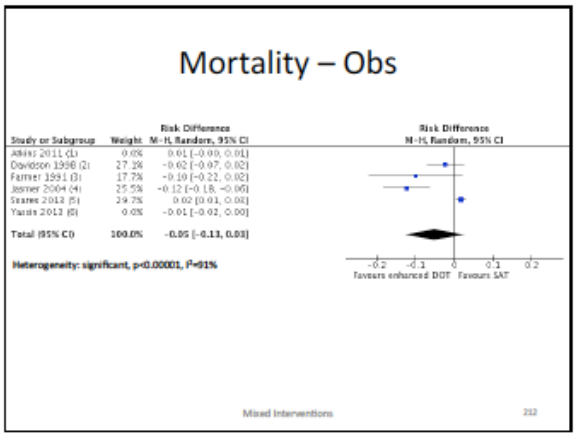
	Selection	Comparability	Outcome
Atkins	4	2	3
Farmer	2	0	3
Jasmer	3	1	2
Soares	3	0	2
Yassin	4	2	3
Chan	4	2	3
Garden	1	0	3
Davidson	4	2	3

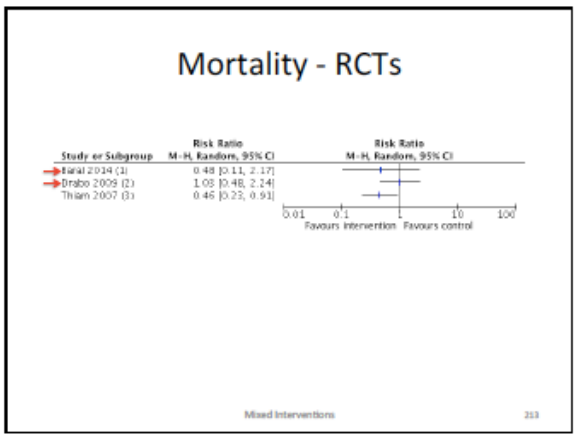
Newcastle Ottawa Scale

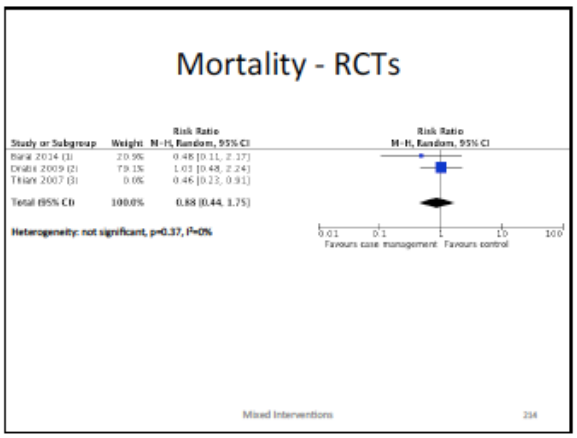
Mortality – Obs

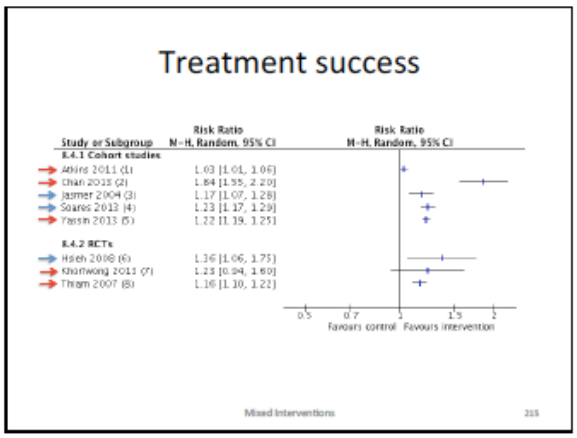


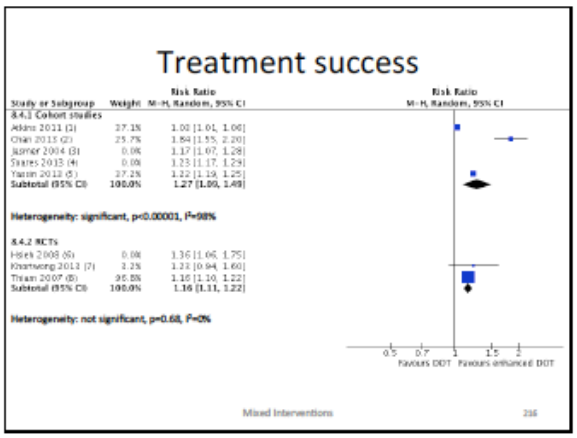

Mortality – Obs
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Atkins 2011 (1) 56.9% 1.09 [0.94, 1.27]
Davidson 1998 (2) 0.0% -0.02 [-0.07, 0.02]
Farmer 1991 (3) 0.0% -0.10 [-0.22, 0.02]
Jasmer 2004 (4) 0.0% -0.12 [-0.18, -0.06]
Soares 2013 (5) 0.0% 0.02 [0.01, 0.03]
Yassin 2013 (6) 43.1% 0.74 [0.54, 1.02]
Total (95% CI) 100.0% 0.93 [0.64, 1.35]
Heterogeneity: significant, p=0.03, I²=78%
0.5 0.7 1 1.5 2
Favours enhanced DOT Favours DOT
Mixed Interventions
211

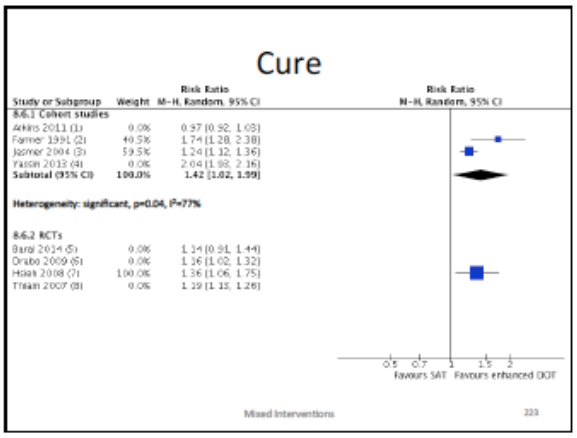

Mortality – Obs
Risk Difference
Risk Difference
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Atkins 2011 (1) 0.0% 0.01 [-0.00, 0.01]
Davidson 1998 (2) 27.2% -0.02 [-0.07, 0.02]
Farmer 1991 (3) 17.7% -0.10 [-0.22, 0.02]
Jasmer 2004 (4) 25.5% -0.12 [-0.18, -0.06]
Soares 2013 (5) 29.5% 0.02 [0.01, 0.03]
Yassin 2013 (6) 0.0% -0.01 [-0.02, 0.00]
Total (95% CI) 100.0% -0.05 [-0.13, 0.03]
Heterogeneity: significant, p<0.00001, I²=91%
-0.2 -0.1 0 0.1 0.2
Favours enhanced DOT Favours SAT
Mixed Interventions
212

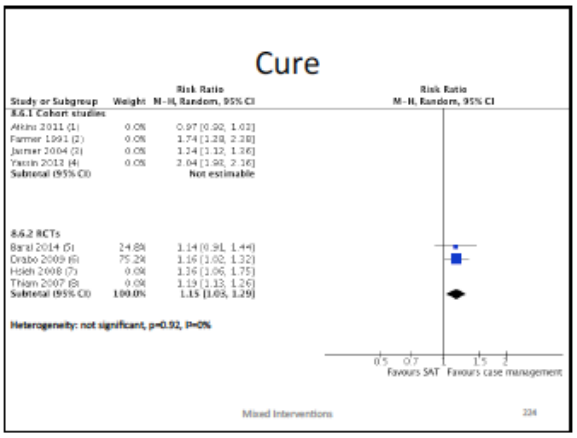

Mortality - RCTs
Risk Ratio
Risk Ratio
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
Barat 2014 (1) 0.48 [0.11, 2.17]
Drabo 2009 (2) 1.03 [0.48, 2.24]
Thiam 2007 (3) 0.46 [0.23, 0.91]
0.01 0.1 1 10 100
Favours intervention Favours control
Mixed Interventions
213

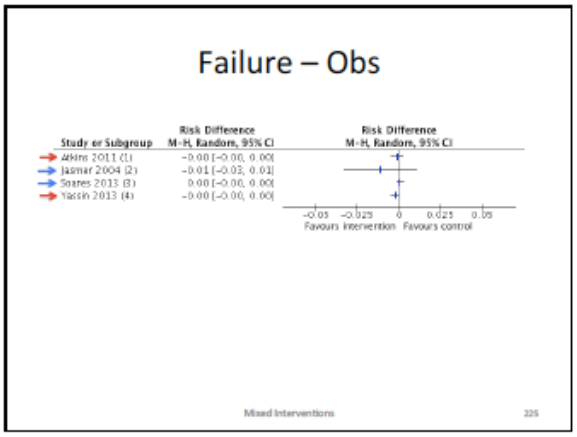

Mortality - RCTs
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Barat 2014 (1) 20.9% 0.48 [0.11, 2.17]
Drabo 2009 (2) 79.1% 1.03 [0.48, 2.24]
Thiam 2007 (3) 0.0% 0.46 [0.23, 0.91]
Total (95% CI) 100.0% 0.88 [0.44, 1.75]
Heterogeneity: not significant, p=0.37, I²=0%
0.01 0.1 1 10 100
Favours case management Favours control
Mixed Interventions
214

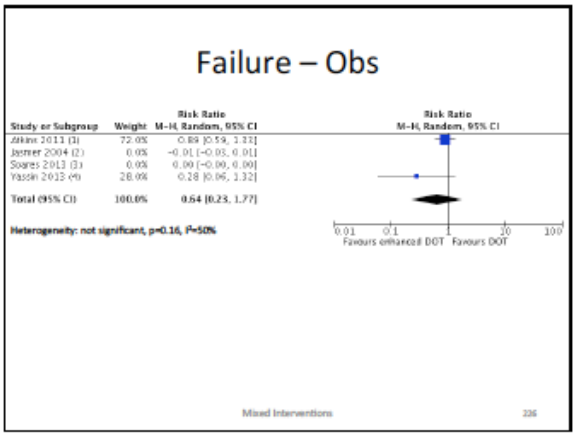

Treatment success
Risk Ratio
Risk Ratio
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
8.4.1 Cohort studies
Atkins 2011 (1) 1.03 [1.01, 1.06]
Chan 2013 (2) 1.84 [1.55, 2.20]
Jasmer 2004 (3) 1.17 [1.07, 1.28]
Soares 2013 (4) 1.23 [1.17, 1.29]
Yassin 2013 (5) 1.22 [1.19, 1.25]
8.4.2 RCTs
Hsieh 2008 (6) 1.36 [1.06, 1.75]
Khamwong 2013 (7) 1.23 [0.94, 1.60]
Thiam 2007 (8) 1.16 [1.10, 1.22]
0.5 0.7 1 1.5 2
Favours control Favours intervention
Mixed Interventions
215

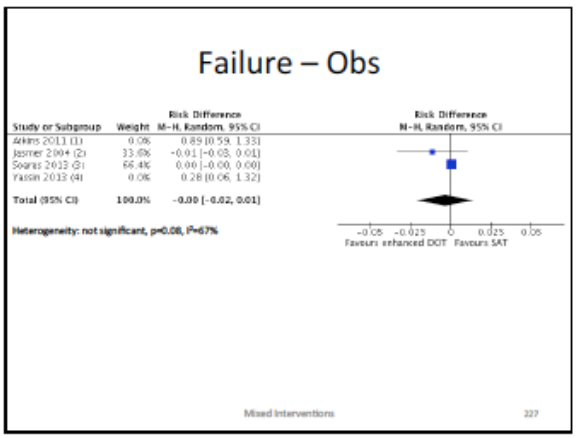

Treatment success
Risk Ratio
Risk Ratio
Study or Subgroup
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
8.4.1 Cohort studies
Atkins 2011 (1) 37.1% 1.03 [1.01, 1.06]
Chan 2013 (2) 25.7% 1.84 [1.55, 2.20]
Jasmer 2004 (3) 0.0% 1.17 [1.07, 1.28]
Soares 2013 (4) 0.0% 1.23 [1.17, 1.29]
Yassin 2013 (5) 37.2% 1.22 [1.19, 1.25]
Subtotal (95% CI) 100.0% 1.27 [1.09, 1.49]
Heterogeneity: significant, p<0.00001, I²=98%
8.4.2 RCTs
Hsieh 2008 (6) 0.0% 1.36 [1.06, 1.75]
Khamwong 2013 (7) 3.2% 1.23 [0.94, 1.60]
Thiam 2007 (8) 96.8% 1.16 [1.10, 1.22]
Subtotal (95% CI) 100.0% 1.16 [1.11, 1.22]
Heterogeneity: not significant, p=0.68, I²=0%
0.5 0.7 1 1.5 2
Favours DOT Favours enhanced DOT
Mixed Interventions
216

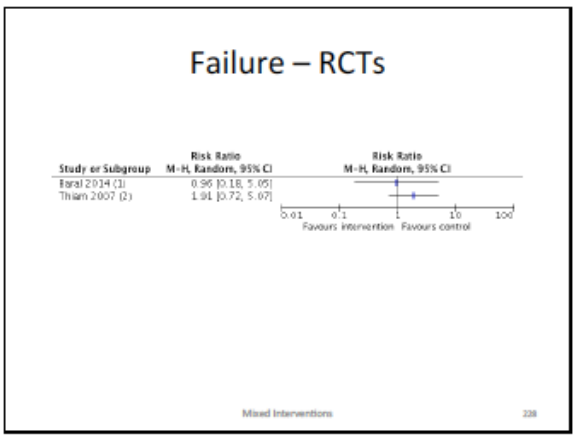

Cure
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.6.1 Cohort studies
Akins 2011 (1) 0.0% 0.97 [0.92, 1.03]
Farmer 1991 (2) 49.5% 1.74 [1.28, 2.38]
Jasmer 2004 (3) 50.5% 1.24 [1.12, 1.36]
Yassin 2013 (4) 0.0% 2.04 [1.98, 2.16]
Subtotal (95% CI) 100.0% 1.42 [1.02, 1.99]
Heterogeneity: significant, p=0.04, I²=77%
8.6.2 RCTs
Baral 2014 (5) 0.0% 1.14 [0.91, 1.44]
Drabo 2009 (6) 0.0% 1.16 [1.02, 1.32]
Hsieh 2008 (7) 100.0% 1.36 [1.06, 1.75]
Thiam 2007 (8) 0.0% 1.19 [1.13, 1.26]
0.5 0.7 1 1.5 2
Favours SAT Favours enhanced DOT
Mixed Interventions
223

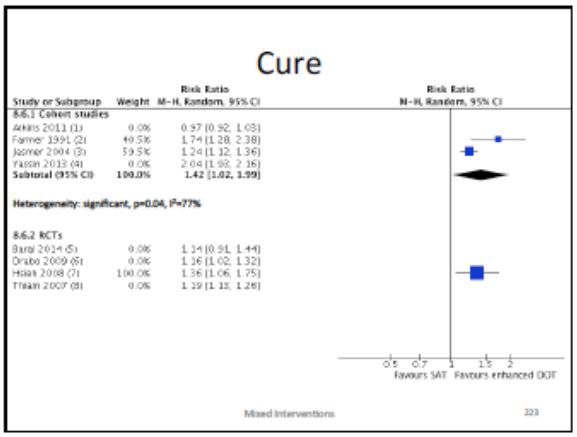

Cure
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.6.1 Cohort studies
Akins 2011 (1) 0.0% 0.97 [0.92, 1.03]
Farmer 1991 (2) 0.0% 1.74 [1.28, 2.38]
Jasmer 2004 (3) 0.0% 1.24 [1.12, 1.36]
Yassin 2013 (4) 0.0% 2.04 [1.98, 2.16]
Subtotal (95% CI) Not estimable
8.6.2 RCTs
Baral 2014 (5) 24.8% 1.14 [0.91, 1.44]
Drabo 2009 (6) 75.2% 1.16 [1.02, 1.32]
Hsieh 2008 (7) 0.0% 1.36 [1.06, 1.75]
Thiam 2007 (8) 0.0% 1.19 [1.13, 1.26]
Subtotal (95% CI) 100.0% 1.15 [1.05, 1.25]
Heterogeneity: not significant, p=0.92, I²=0%
0.5 0.7 1 1.5 2
Favours SAT Favours case management
Mixed Interventions
224

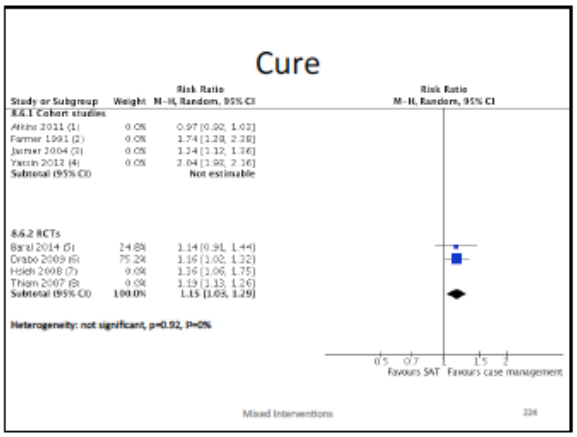

Failure – Obs
Risk Difference
Risk Difference
Study or Subgroup M-H, Random, 95% CI
M-H, Random, 95% CI
Akins 2011 (1) -0.00 [-0.00, 0.00]
Jasmer 2004 (2) -0.01 [-0.03, 0.01]
Soares 2013 (3) 0.00 [-0.00, 0.00]
Yassin 2013 (4) -0.00 [-0.00, 0.00]
-0.05 -0.025 0 0.025 0.05
Favours intervention Favours control
Mixed Interventions
225

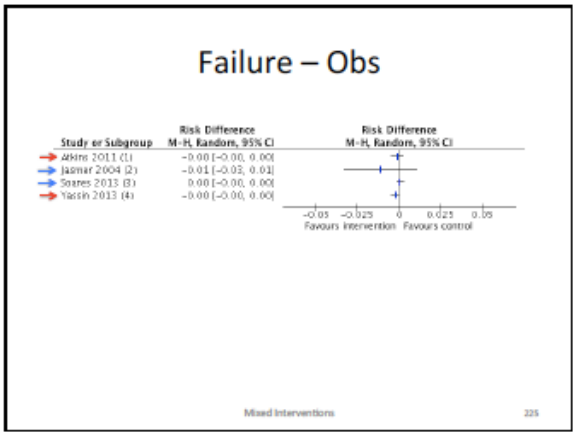

Failure – Obs
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Akins 2011 (1) 72.0% 0.89 [0.59, 1.33]
Jasmer 2004 (2) 0.0% -0.01 [-0.03, 0.01]
Soares 2013 (3) 0.0% 0.00 [-0.00, 0.00]
Yassin 2013 (4) 28.0% 0.28 [0.06, 1.32]
Total (95% CI) 100.0% 0.64 [0.23, 1.77]
Heterogeneity: not significant, p=0.16, I²=50%
0.01 0.1 1 10 100
Favours enhanced DOT Favours DOT
Mixed Interventions
226

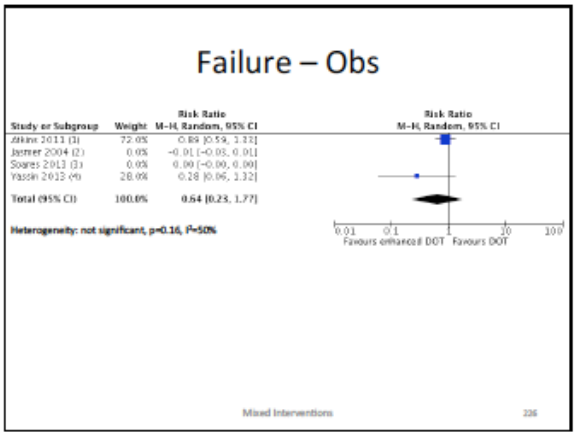

Failure – Obs
Risk Difference
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Akins 2011 (1) 0.0% 0.89 [0.59, 1.33]
Jasmer 2004 (2) 33.6% -0.01 [-0.03, 0.01]
Soares 2013 (3) 66.4% 0.00 [-0.00, 0.00]
Yassin 2013 (4) 0.0% 0.28 [0.06, 1.32]
Total (95% CI) 100.0% -0.00 [-0.02, 0.01]
Heterogeneity: not significant, p=0.08, I²=67%
-0.05 -0.025 0 0.025 0.05
Favours enhanced DOT Favours SAT
Mixed Interventions
227

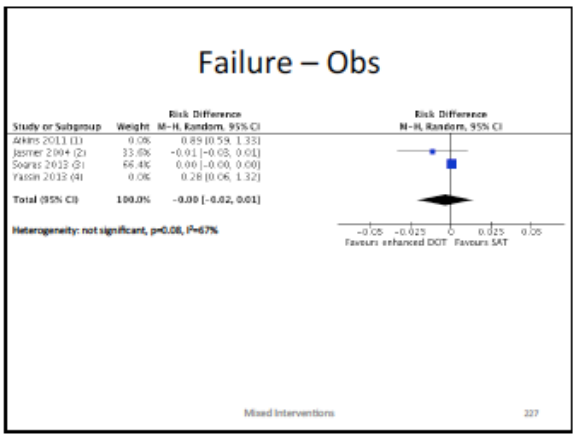

Failure – RCTs
Risk Ratio
Risk Ratio
Study or Subgroup M-H, Random, 95% CI
M-H, Random, 95% CI
Baral 2014 (1) 0.96 [0.18, 5.05]
Thiam 2007 (2) 1.91 [0.72, 5.07]
0.01 0.1 1 10 100
Favours intervention Favours control
Mixed Interventions
228

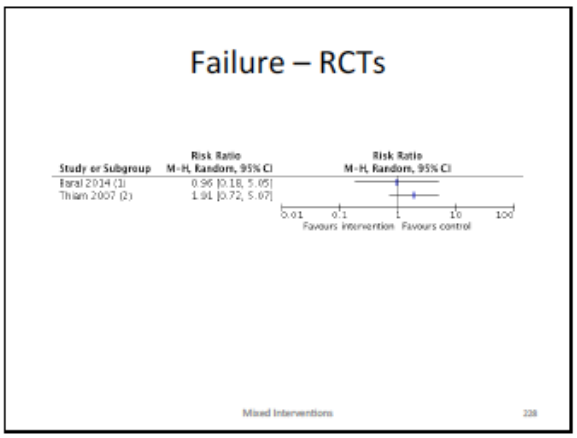

Cure
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.6.1 Cohort studies
Akins 2011 (1) 0.0% 0.97 [0.92, 1.03]
Farmer 1991 (2) 40.5% 1.74 [1.28, 2.38]
Jasmer 2004 (3) 59.5% 1.24 [1.12, 1.36]
Yassin 2013 (4) 0.0% 2.04 [1.98, 2.16]
Subtotal (95% CI) 100.0% 1.42 [1.02, 1.99]
Heterogeneity: significant, p=0.04, I²=77%
8.6.2 RCTs
Baral 2014 (5) 0.0% 1.14 [0.91, 1.44]
Drabo 2009 (6) 0.0% 1.16 [1.02, 1.32]
Hsieh 2008 (7) 100.0% 1.36 [1.06, 1.75]
Thiam 2007 (8) 0.0% 1.19 [1.13, 1.26]
0.5 0.7 1 1.5 2
Favours SAT Favours enhanced DOT
Mixed Interventions
223


Cure
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
8.6.1 Cohort studies
Akins 2011 (1) 0.0% 0.97 [0.92, 1.03]
Farmer 1991 (2) 0.0% 1.74 [1.28, 2.38]
Jasmer 2004 (3) 0.0% 1.24 [1.12, 1.36]
Yassin 2013 (4) 0.0% 2.04 [1.98, 2.16]
Subtotal (95% CI) Not estimable
8.6.2 RCTs
Baral 2014 (5) 24.8% 1.14 [0.91, 1.44]
Drabo 2009 (6) 75.2% 1.16 [1.02, 1.32]
Hsieh 2008 (7) 0.0% 1.36 [1.06, 1.75]
Thiam 2007 (8) 0.0% 1.19 [1.13, 1.26]
Subtotal (95% CI) 100.0% 1.15 [1.05, 1.25]
Heterogeneity: not significant, p=0.92, I²=0%
0.5 0.7 1 1.5 2
Favours SAT Favours case management
Mixed Interventions
224

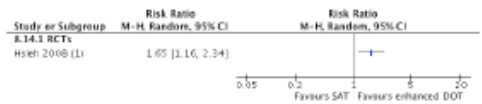

Failure – Obs
Risk Difference
Risk Difference
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
Akins 2011 (1) -0.00 [-0.00, 0.00]
Jasmer 2004 (2) -0.01 [-0.03, 0.01]
Soares 2013 (3) 0.00 [-0.00, 0.00]
Yassin 2013 (4) -0.00 [-0.00, 0.00]
-0.05 -0.025 0 0.025 0.05
Favours intervention Favours control
Mixed Interventions
225


Failure – Obs
Risk Ratio
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Akins 2011 (1) 72.0% 0.89 [0.59, 1.33]
Jasmer 2004 (2) 0.0% -0.01 [-0.03, 0.01]
Soares 2013 (3) 0.0% 0.00 [-0.00, 0.00]
Yassin 2013 (4) 28.0% 0.28 [0.06, 1.32]
Total (95% CI) 100.0% 0.64 [0.23, 1.77]
Heterogeneity: not significant, p=0.16, I²=50%
0.01 0.1 1 10 100
Favours enhanced DOT Favours DOT
Mixed Interventions
226


Failure – Obs
Risk Difference
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Akins 2011 (1) 0.0% 0.89 [0.59, 1.33]
Jasmer 2004 (2) 33.6% -0.01 [-0.03, 0.01]
Soares 2013 (3) 66.4% 0.00 [-0.00, 0.00]
Yassin 2013 (4) 0.0% 0.28 [0.06, 1.32]
Total (95% CI) 100.0% -0.00 [-0.02, 0.01]
Heterogeneity: not significant, p=0.08, I²=67%
-0.05 -0.025 0 0.025 0.05
Favours enhanced DOT Favours SAT
Mixed Interventions
227

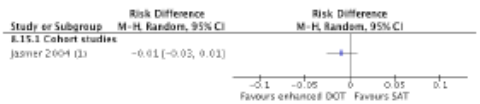

Failure – RCTs
Risk Ratio
Risk Ratio
Study or Subgroup
M-H, Random, 95% CI
M-H, Random, 95% CI
Baral 2014 (1) 0.96 [0.18, 5.05]
Thiam 2007 (2) 1.91 [0.72, 5.07]
0.01 0.1 1 10 100
Favours intervention Favours control
Mixed Interventions
228

Sputum conversion rate



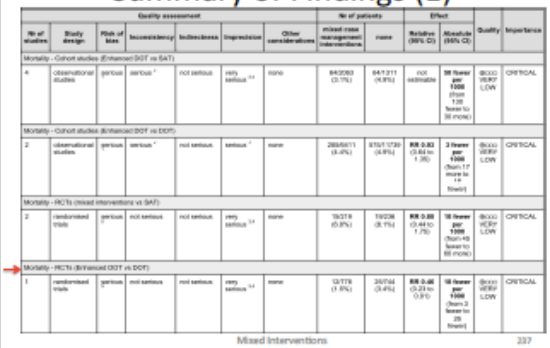
Mixed Interventions 235

Acquired drug resistance



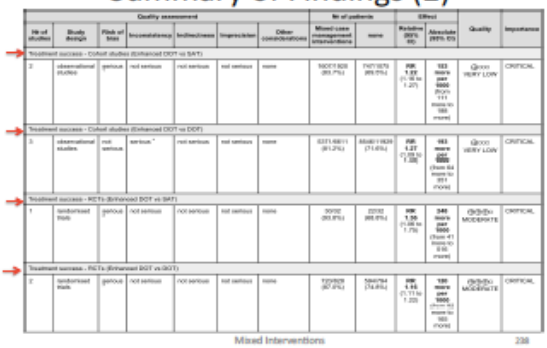
Mixed Interventions 236

Summary of Findings (1)



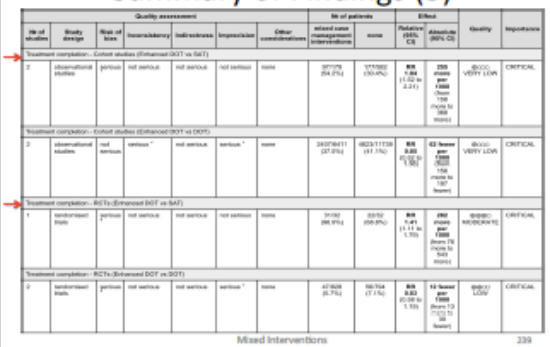
Mixed Interventions 237

Summary of Findings (2)



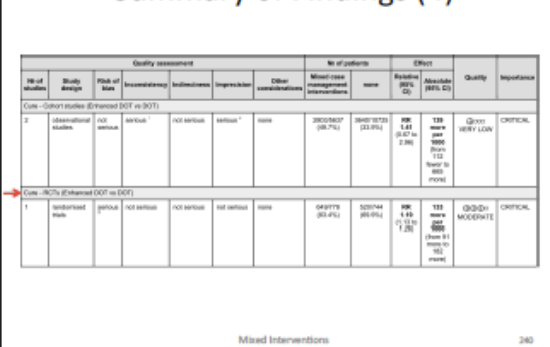
Mixed Interventions 238

Summary of Findings (3)



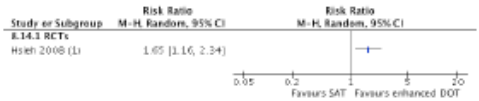
Mixed Interventions 239

Summary of Findings (4)



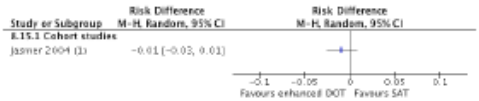
Mixed Interventions 240

Sputum conversion rate



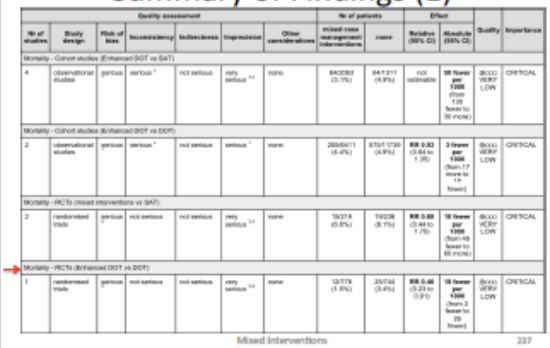
Mixed Interventions 235

Acquired drug resistance



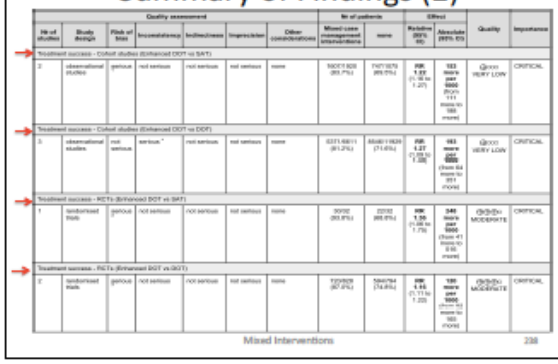
Mixed Interventions 236

Summary of Findings (1)



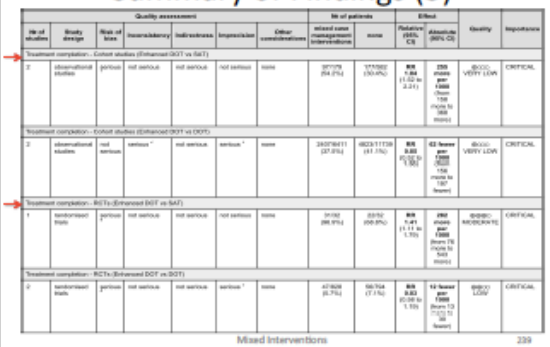
Mixed Interventions 237

Summary of Findings (2)



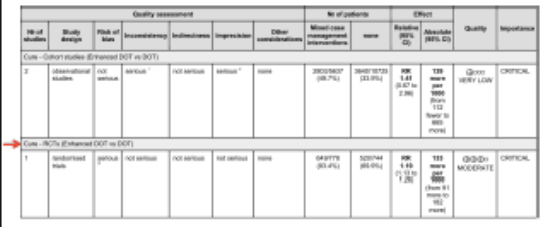
Mixed Interventions 238

Summary of Findings (3)



Mixed Interventions 239

Summary of Findings (4)



Mixed Interventions 240

Psychosocial

247

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	Intervention
Shin	2013	RCT	Russia	196	-≥ 18 years old -TB/HIV -New & retreatment	Brief counseling intervention for ETOH cessation
Alvarez	2003	RCT	Mexico	87	-≥15 years old -PTB	Self-help groups

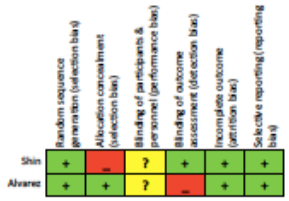
Psychosocial Interventions 248

Observational study

Author	Year	Study design	Country	# of patients	Condition	Intervention
Demissie	2003	Prospective	Ethiopia	128	-Adults & children -PTB (smear +/-)	TB clubs as a support network

Psychosocial Interventions 249

Quality – RCTs



Cochrane risk of bias tool

Psychosocial Interventions 250

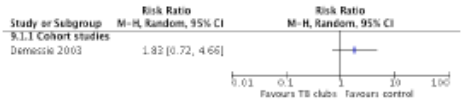
Quality – Obs

	Selection	Comparability	Outcome
Demissie	3	2	3

Newcastle Ottawa Scale

Psychosocial Interventions 251

Mortality



Psychosocial Interventions 252

Psychosocial

247

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	Intervention
Shin	2013	RCT	Russia	196	-≥ 18 years old -TB/HIV -New & retreatment	Brief counseling intervention for ETOH cessation
Alvarez	2003	RCT	Mexico	87	-≥15 years old -PTB	Self-help groups

Psychosocial Interventions 248

Observational study

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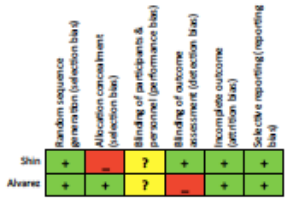
Psychosocial Interventions 249

Quality – RCTs



Cochrane risk of bias tool

Psychosocial Interventions 250

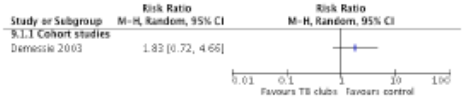
Quality – Obs

	Selection	Comparability	Outcome
Demissie	3	2	3

Newcastle Ottawa Scale

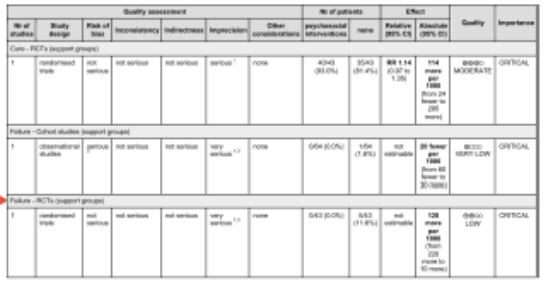
Psychosocial Interventions 251

Mortality



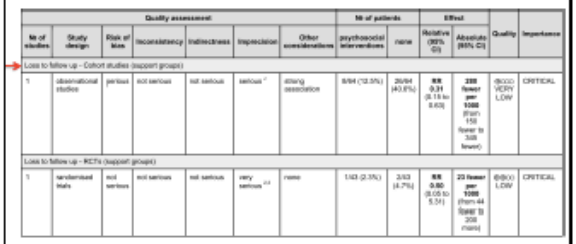
Psychosocial Interventions 252

Summary of Findings (2)



Psychosocial Interventions 259

Summary of Findings (3)



Psychosocial Interventions 260

Conclusions

- Higher rate of treatment completion and lower rate of treatment failure and loss to follow up with psychosocial interventions (support groups)

Psychosocial Interventions 261

Staff education

262

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	Intervention
Lewin	2005	RCT	South Africa	1177	-≥14 years -PTB (smear +) -New -Excluded MDR-TB	-Adherence education for staff
Ritchie	2015	RCT	Malawi	176	-New -Adults & children -PTB -EPTB -TB/HIV (45%)	-Peer training of LHW -Laminated chart/visual reminder to initiate adherence discussions
Datiko	2009	RCT	Ethiopia	318	-New -PTB (smear +) -Adults & children	-Education for HCW and lab techs

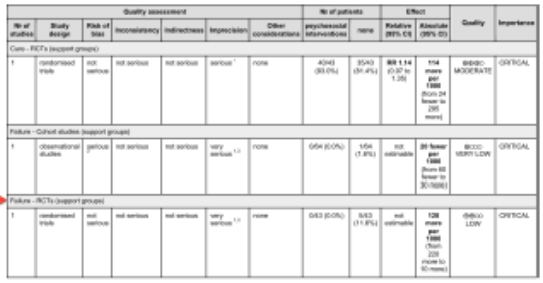
Staff Education 263

Observational study

Author	Year	Study design	Country	# of patients	Condition	Intervention
Safdar	2011	Prospective	Pakistan	194	-Children (100%) -PTB (smear +/-) -EPTB	-Staff educational tool and desktop aid for decision making and red flags

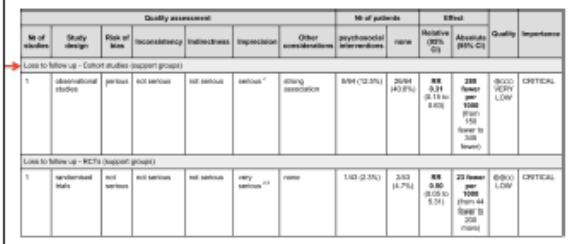
Staff Education 264

Summary of Findings (2)



Psychosocial Interventions 259

Summary of Findings (3)



Psychosocial Interventions 260

Conclusions

- Higher rate of treatment completion and lower rate of treatment failure and loss to follow up with psychosocial interventions (support groups)

Psychosocial Interventions 261

Staff education

262

Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	Intervention
Lewin	2005	RCT	South Africa	1177	-≥14 years -PTB (smear +) -New -Excluded MDR-TB	-Adherence education for staff
Ritchie	2015	RCT	Malawi	176	-New -Adults & children -PTB -EPTB -TB/HIV (45%)	-Peer training of LHW -Laminated chart/visual reminder to initiate adherence discussions
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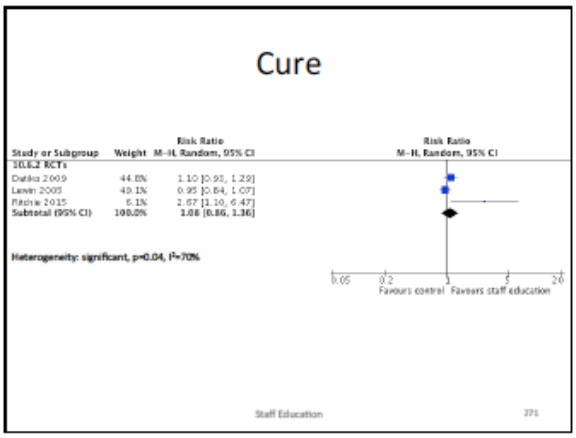
Staff Education 263

Observational study

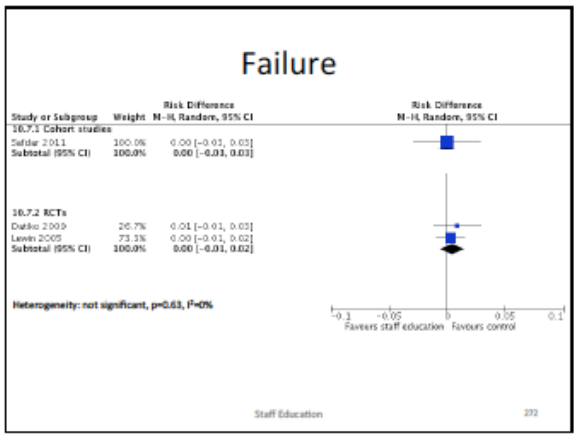
Author	Year	Study design	Country	# of patients	Condition	Intervention
Safdar	2011	Prospective	Pakistan	194	-Children (100%) -PTB (smear +/-) -EPTB	-Staff educational tool and desktop aid for decision making and red flags

Staff Education 264

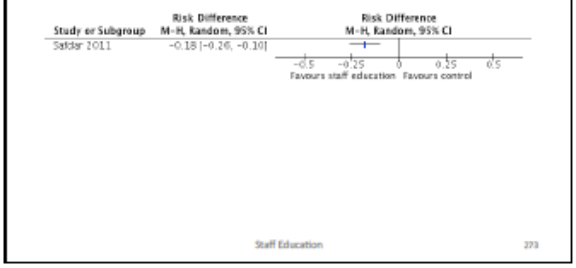
Cure



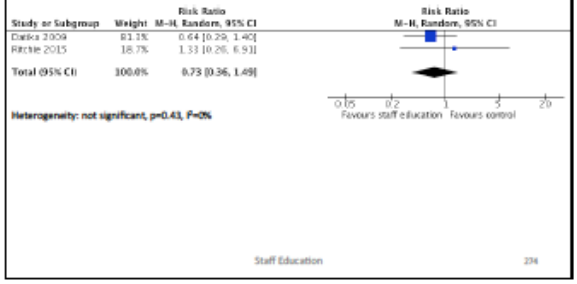
Failure



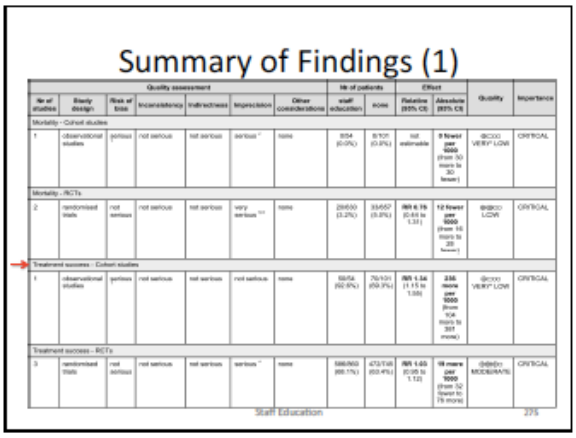
Loss to follow up – Obs



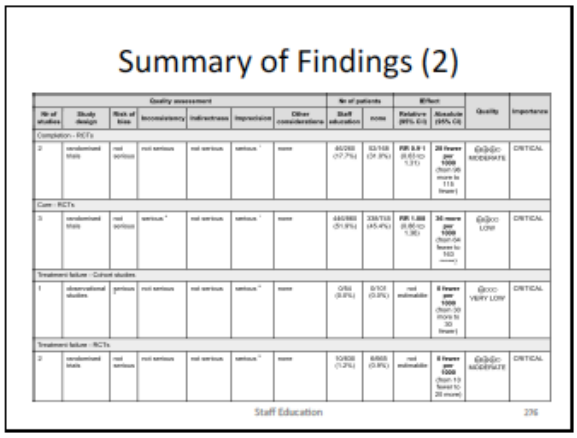
Loss to follow up – RCTs

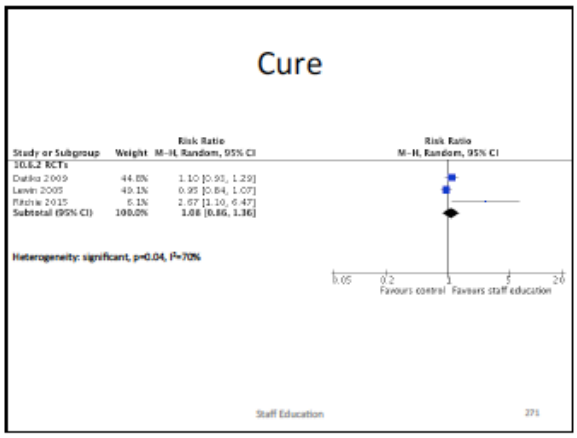


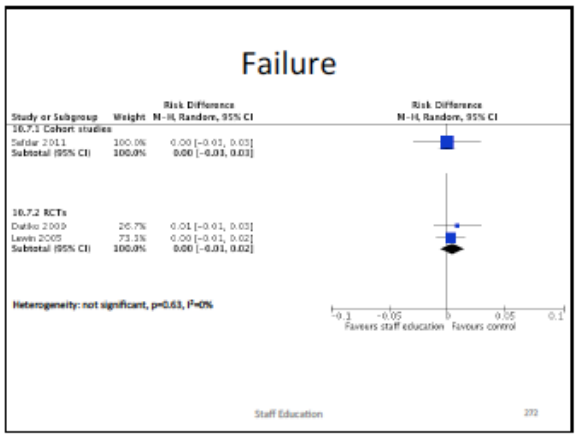
Summary of Findings (1)

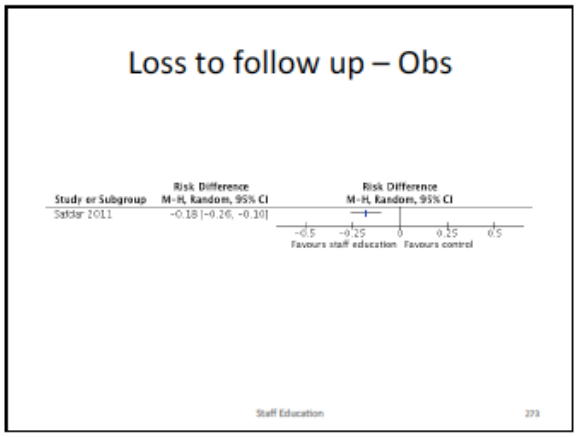


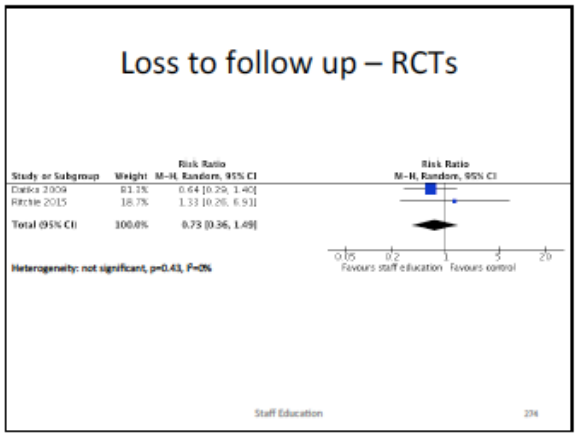
Summary of Findings (2)

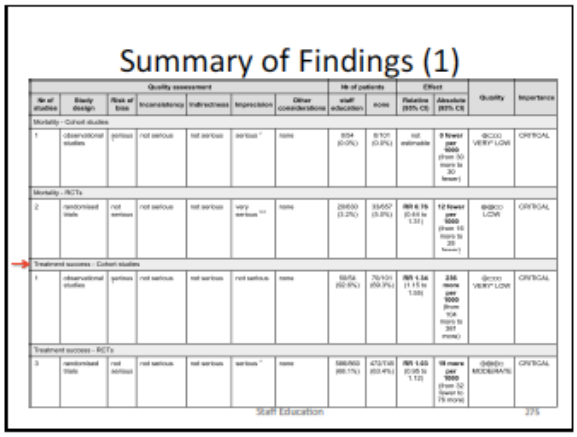


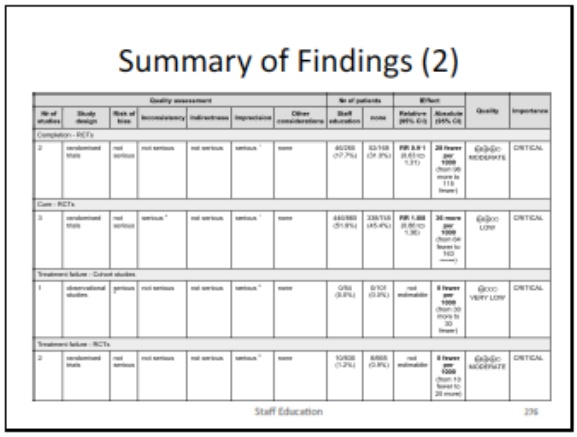

Cure
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
10.6.2 RCTs
Datiko 2009 44.8% 1.10 [0.93, 1.29]
Lewin 2005 49.1% 0.93 [0.84, 1.03]
Ritchie 2015 6.1% 2.67 [1.10, 6.47]
Subtotal (95% CI) 100.0% 1.08 [0.86, 1.36]
Heterogeneity: significant, p=0.04, I²=70%
Risk Ratio
M-H, Random, 95% CI
0.05 0.2 1 5 20
Favours control Favours staff education
Staff Education
271


Failure
Risk Difference
Study or Subgroup Weight M-H, Random, 95% CI
10.7.1 Cohort studies
Sidibe 2011 100.0% 0.00 [-0.01, 0.01]
Subtotal (95% CI) 100.0% 0.00 [-0.01, 0.01]
10.7.2 RCTs
Datiko 2009 26.7% 0.01 [-0.01, 0.03]
Lewin 2005 73.3% 0.00 [-0.01, 0.02]
Subtotal (95% CI) 100.0% 0.00 [-0.01, 0.02]
Heterogeneity: not significant, p=0.63, I²=0%
Risk Difference
M-H, Random, 95% CI
-0.1 -0.05 0 0.05 0.1
Favours staff education Favours control
Staff Education
272


Loss to follow up – Obs
Risk Difference
Study or Subgroup M-H, Random, 95% CI
Sidibe 2011 -0.18 [-0.26, -0.10]
Risk Difference
M-H, Random, 95% CI
-0.5 -0.25 0 0.25 0.5
Favours staff education Favours control
Staff Education
273


Loss to follow up – RCTs
Risk Ratio
Study or Subgroup Weight M-H, Random, 95% CI
Datiko 2009 81.3% 0.64 [0.29, 1.40]
Ritchie 2015 18.7% 1.33 [0.26, 6.91]
Total (95% CI) 100.0% 0.73 [0.36, 1.49]
Heterogeneity: not significant, p=0.43, I²=0%
Risk Ratio
M-H, Random, 95% CI
0.05 0.2 1 5 20
Favours staff education Favours control
Staff Education
274


Summary of Findings (1)
Staff Education
275


Summary of Findings (2)
Staff Education
276

Summary of Findings (3)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	staff education	none	Relative (95% CI)	Absolute (95% CI)		
Loss to follow up – Cohort studies												
1	observational studies	serious	not serious	not serious	serious [1]	none	6/54 (0.0%)	19/101 (17.8%)	not estimable	188 fewer per 1000 (from 268 fewer to 108 fewer)	⊕○○○ VERY LOW	CRITICAL
Loss to follow up – RCTs												
2	randomised trials	not serious	not serious	not serious	very serious [1,2]	none	17/260 (6.5%)	13/166 (7.7%)	RR 6.74 (0.36 to 1.49)	39 fewer per 1000 (from 28 more to 50 fewer)	⊕○○○ LOW	CRITICAL

Conclusion

- Higher rate of treatment success and lower rate of loss to follow up with staff education interventions

Mobile health

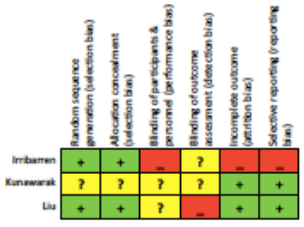
Randomized controlled trials

Author	Year	Study design	Country	# of patients	Condition	Intervention
Iribarren	2013	RCT	Argentina	37	-New -≥ 18 years -PTB (smear +)	Patients text daily after taking meds and received reminder texts.
Kunawarak	2011	RCT	Thailand	61	-New -PTB (smear +)	Family-DOT + daily phone call reminder to take meds
Liu	2015	RCT	China	4173	-New -PTB (smear +/-) -≥ 18 years	-SMS -Med monitor -Both -Control

Observational study

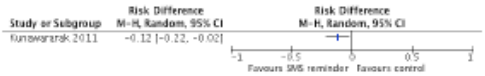
Author	Year	Study design	Country	# of patients	Condition	Intervention
Chuck	2016	Prospective	USA	300	-≥18 years -PTB (smear +/-) -included drug resistant -included TB-HIV	-VDOT vs in-person DOT
Broomhead	2012	Case-control	South Africa	120	-PTB (smear +) -New	-Wireless pill box with alarm system sends SMS -DOTS
Wade	2012	Retrospective	Australia	128	-Anyone receiving DOT	-home videophone DOT vs in-person DOT

Quality – RCTs

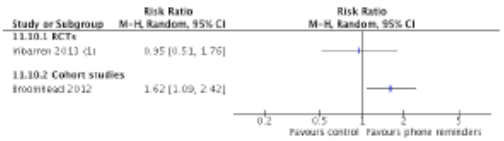


Cochrane risk of bias tool

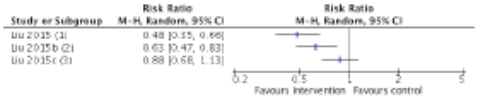
Failure



Sputum conversion rate

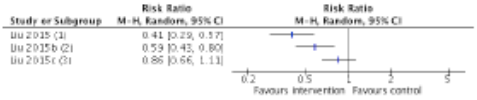


Poor outcome



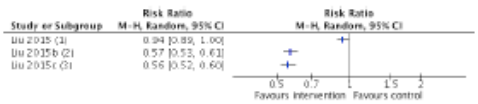
Footnotes
(1) control vs SMS
(2) Med monitor vs control
(3) med monitor + SMS vs control

Loss to follow up



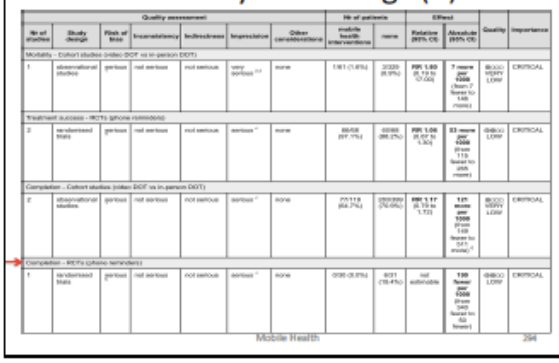
Footnotes
(1) SMS vs control
(2) Med monitor vs control
(3) Combined med monitor vs control

Poor adherence

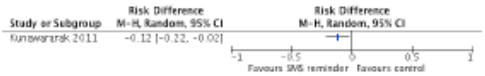


Footnotes
(1) SMS vs control
(2) Medation monitor vs control
(3) SMS and medication monitor vs control

Summary of Findings (1)



Failure



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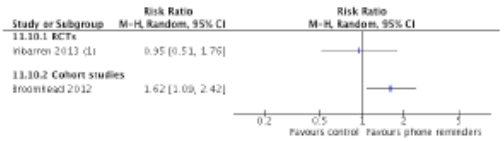
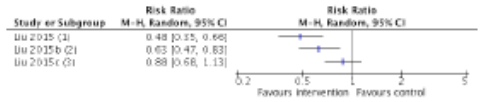
Sputum conversion rate



Mobile Health 290

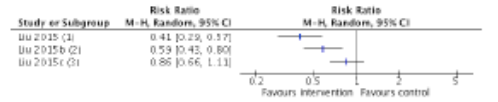
Poor outcome



Footnotes
(1) control vs SMS
(2) Med monitor vs control
(3) med monitor + SMS vs control

Mobile Health 291

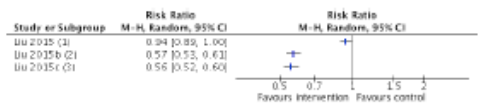
Loss to follow up



Footnotes
(1) SMS vs control
(2) Med monitor vs control
(3) Combined med monitor vs control

Mobile Health 292

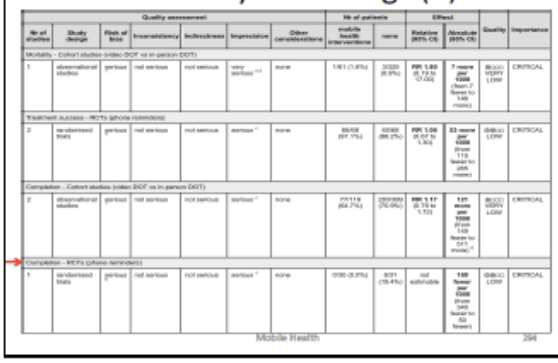
Poor adherence



Footnotes
(1) SMS vs control
(2) Medation monitor vs control
(3) SMS and medication monitor vs control

Mobile Health 293

Summary of Findings (1)



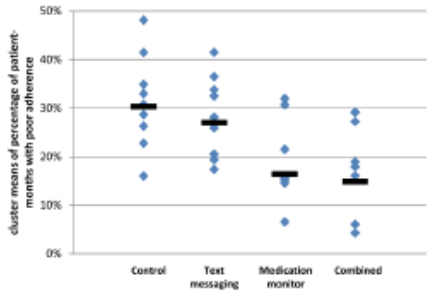
Mobile Health 294

Liu et al – Study design

- PLoS One. 2015
- RCT, cluster randomized
- Inclusion criteria:
  - New patients
  - ≥18 years
- Intervention:
  - SMS reminder
  - Med monitor box reminder
  - Both
- Control:
  - SAT, family DOT, or HCW DOT (per patient preference)
- Outcomes:
  - Number of missed doses based on pill count
  - Poor adherence = Percentage of patient-months where ≥ 20% of doses were missed

Mobile Health 301

Liu et al – Results



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Liu et al – Results

Table 3. Effectiveness of interventions on tuberculosis treatment adherence and treatment outcomes endpoints.

Endpoint and Study Arm	Number of Patients	Geometric Mean of Cluster-Level Endpoint	Unadjusted Analysis		Adjusted Analysis[1]	
			MR (95% CI)	p-Value	MR (95% CI)	p-Value
Primary endpoint—percentage of patient-months with at least 20% doses missed[2,3,4]						
Control	1,891	29.9%	1		1	
Text messaging	936	27.3%	0.91 (0.66, 1.25)	0.536	0.94 (0.71, 1.24)	0.622
Medication monitor	992	17.0%	0.57 (0.40, 0.81)	0.004	0.58 (0.42, 0.79)	0.002
Combined	1,059	13.9%	0.46 (0.25, 0.84)	0.018	0.49 (0.27, 0.88)	0.020
Poor treatment outcome (treatment failure, death, or patient loss to follow-up)[3]						
Control	1,966	8.8%	1		1	
Text messaging	968	3.8%	0.46 (0.19, 1.16)	0.097	0.44 (0.17, 1.13)	0.084
Medication monitor	955	6.1%	0.76 (0.32, 1.53)	0.264	0.71 (0.33, 1.51)	0.346
Combined	992	8.8%	1.01 (0.46, 2.22)	0.973	1.09 (0.49, 2.29)	0.891
Patient loss to follow-up[3]						
Control	1,957	8.5%	1		1	
Text messaging	954	3.8%	0.40 (0.16, 1.00)	0.050	0.42 (0.18, 0.98)	0.046
Medication monitor	948	5.0%	0.58 (0.23, 1.51)	0.263	0.61 (0.25, 1.51)	0.284
Combined	982	7.6%	0.90 (0.38, 2.08)	0.783	0.90 (0.38, 2.09)	0.784

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Decentralised Treatment and Care for Multi-Drug Resistant Tuberculosis Patients

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Executive summary

Background

Multi-drug resistant tuberculosis (MDR-TB) poses a major threat to the control of TB worldwide. Management of MDR-TB is complex and prolonged, and has traditionally been provided in centralised specialised treatment centres. However, such treatment centres are insufficient to meet the needs of the large and growing burden of MDR-TB patients in most settings. Decentralised treatment typically utilises facilities close to the patient's residential location (including home-based care), and trained personnel in the community to administer and monitor treatment, thereby overcoming the resource limitations in centralised, specialised facilities. In this review we summarise the evidence for the use of decentralised treatment and care for patients with MDR-TB.

Methods

We performed a comprehensive database search for relevant studies on decentralised treatment and care for patients with MDR-TB, which compared treatment outcomes, treatment adherence and cost to health services, to centralised treatment facilities. For outcome measures which had sufficient studies, a meta-analysis was performed to obtain pooled relative risk (RR) estimates.

Results

Eight studies comprising of 4,493 patients with MDR-TB were eligible for review inclusion. Two studies modelled cost-effectiveness, whilst the remaining six cohort studies reported on treatment outcomes and/or cost of health-care. The pooled RR estimates for decentralised versus centralised care for the outcomes of treatment success, loss to follow-up, death and treatment failure were: 1.13 (95% CI 1.01-1.27), 0.66 (95%CI 0.38-1.13), 1.01 (95% CI 0.67-1.52) and 1.07 (95%CI 0.48-2.40) respectively. Considerable study heterogeneity was seen amongst the studies for each pooled estimate.

Conclusions

Treatment success for MDR-TB patients improved when patients were treated in a decentralised, compared to centralised, setting. Further studies, in a range of different settings, are required to improve the evidence base for recommending decentralised care for patients with MDR-TB.

Background

Multi-drug resistant tuberculosis (MDR-TB) (i.e. resistance to both rifampicin and isoniazid) poses a major threat to the control of TB worldwide. In 2014, there were an estimated 480,000 new cases of MDR-TB worldwide and approximately 190,000 deaths from MDR-TB.[1] An estimated 9.7% of people with MDR-TB have extensively drug resistant TB (XDR-TB) (i.e. MDR-TB that is also resistant to a second line injectable drug and a fluoroquinolone). Of all MDR-TB cases from the 2012 cohort, only 50% completed treatment, 16% died, 16% were lost to follow-up and treatment failed for 10%.[1] Recommended therapy for MDR-TB requires a combination of second-line drugs that are more costly, less efficacious, more toxic and must be taken for much longer than first-line TB therapy.[2] Historically MDR-TB treatment has been provided through specialised, centralised programmes, and involved prolonged inpatient care.[3] This approach is based on the view that treatment adherence, the management of adverse events and infection control may be superior in the hospital setting compared to in the community.[4, 5] However, prolonged treatment in centralised facilities is impractical in resource-limited settings, with a substantial number of patients with MDR-TB. Paradoxically, the reliance on centralised treatment for MDR-TB may inadvertently increase transmission of this infection by delaying treatment commencement until inpatient beds become available. In addition, centralised approaches have been associated with poorer rates of retention in care.[6] Decentralised care for the treatment of drug susceptible TB is well-established, with treatment outcomes shown to be at least as good as hospital-based approaches.[7-9] This review aims to evaluate the existing evidence for decentralised care to treat MDR-TB.

Current World Health Organisation Policy

The World Health Organisation (WHO) currently recommends that 'patients with MDR-TB should be treated using mainly ambulatory care, rather than models of care based principally on hospitalization'.[10] These recommendations are 'conditional', reflecting the very low quality evidence upon which they were based. Two published systematic reviews have compared treatment outcomes for hospital and ambulatory-based management of MDR-TB, reporting similar treatment outcomes for centralised and decentralised approaches[11, 12] However, an important limitation of both these reviews was the inclusion of studies without an appropriate comparator group (i.e. a control group, where standard centralised care was provided). The review by Weiss et al,[12] compared pooled treatment outcomes of a community-based MDR-TB management intervention to pooled treatment outcomes from other previously published systematic reviews. Just one of the 41 studies included in one or both of these reviews directly compared hospital and ambulatory MDR-TB care.[13] The approach used in these systematic reviews likely results in substantial bias – given that the control and intervention populations were largely drawn from different study populations. Where possible, direct comparisons should be used to draw conclusions about complex health system interventions.[14] Therefore, more robust evidence is required to evaluate the effect of decentralised care upon treatment outcomes, compared to standard centralised treatment.

Objective of this review

The objective of this review is to examine the effect of decentralized treatment and care upon treatment outcomes among patients with MDR-TB. This review addresses some of the limitations of previous systematic reviews on this topic[11, 12] by including studies that directly compare decentralised and centralised MDR-TB treatment models in the same study setting. This review will contribute to revised WHO guidelines for the treatment of drug resistant TB.

Table 1 provides information about previous related systematic reviews and how these differ from this current review.

Table 1: Summary of related systematic reviews on treatment outcomes for MDR-TB and/or decentralised care for TB

Review	Objective	Main study findings	How this review differs from ours
Studies of DS-TB			
Karumbi et al[15] (2015) (Cochrane review)	Compared treatment outcomes using DOT versus SAT	Found no difference in treatment outcomes for - DOT versus SAT - home versus health facility DOT - family member versus CHW provider	Did not focus on MDR-TB
Wright et al[16] (2015)	Compared treatment outcomes for community based and clinic DOT	Greater treatment success for community versus clinic based DOT	Did not focus on MDR-TB
Kangovi et al[17] (2009)	Compared treatment outcomes using community based DOT programs that do and do not offer financial rewards	No difference in treatment outcomes with and without financial rewards	Did not focus on MDR-TB
Studies of MDR-TB			
Yin et al[18] (2016)	Compared treatment success with DOT to SAT for MDR-TB	Greater treatment success for DOT over the entire treatment course. No difference found between health facility and home based DOT	Did not specifically focus on decentralised versus centralised treatment. The only outcome measured was treatment success.
Toczek et al[6] (2012)	Identified strategies for reducing treatment default in DR-TB	Lower default rates for patients where: CHW provided care, and DOT was given for the entire treatment course	Did not specifically focus on decentralised versus centralised treatment. The only outcome measured was treatment default.
Orenstein et al[19] (2009)	Identified factors associated with improved treatment outcomes in MDR-TB	Improved treatment success with at least 18 months of treatment and DOT for entire course	Did not compare decentralised and centralised treatment.
Johnston et al[20] (2009)	Identified factors associated with poor treatment outcomes in MDR-TB	Factors associated with lower success rates were: male, alcohol abuse, low BMI, smear positive at diagnosis, FQ resistance.	Did not compare decentralised and centralised treatment.
Fitzpatrick et al[21] (2012)	Summarized evidence regarding the cost-effectiveness of MDR-TB treatment.	Treatment for MDR-TB can be cost effective in low- and middle income countries	Did not compare decentralised and centralised treatment.

Weiss et al[12] (2014)	Reviewed treatment outcomes from community based MDR-TB treatment programs	Treatment outcomes of community based MDR-TB treatment were similar to pooled outcomes in published systematic reviews of MDR-TB treatment	Only one included study had a control group. The control group was derived from published systematic reviews on MDR-TB (i.e. different studies)
Bassili et al[11] (2013)	Compared treatment outcomes using ambulatory versus hospital-based MDR-TB treatment	No difference in treatment success between the ambulatory and hospital-based treatment.	Included studies reported either hospital or ambulatory treatment. They did not directly compare outcomes from these two treatment interventions

DS-TB = drug susceptible tuberculosis; DOT = directly observed therapy; SAT = self-administered treatment; CHW = community health worker; MDR-TB = multi-drug resistant tuberculosis; DR-TB = drug resistant tuberculosis; BMI = body mass index; FQ = fluoroquinolone

Definitions

The following definitions are modified from the WHO guidelines for the programmatic management of MDR-TB, 2012.[10] In this review, centralised vs decentralised treatment is defined according to (a) the location of treatment; and/or (b) community-based personnel delivering the treatment. This acknowledges the potential impact of the distance between the treatment facility and patients' residential location upon treatment outcomes and cost, as well as the limited personnel available to provide treatment and care in centralised, specialised settings.

- *Decentralised MDR-TB treatment and care*:
  This refers to treatment and care located in the local community in which the patient resides. This includes treatment delivery based at community health centres, clinics, religious and other community venues, as well as in the patient's home or workplace. The entire treatment period typically occurs in the ambulatory setting, or alternatively, there is a brief period of hospitalisation in a centralised facility (i.e. less than 1 month) that occurs in the intensive phase in order to observe initial response to therapy, manage severe medication side effects or other co-morbid conditions. Decentralised care is delivered primarily by trained volunteers (including family members), community nurses or non-specialised doctors.
- *Specialised/centralised MDR-TB treatment and care*:
  This includes treatment and care in a centralised and/or specialised hospital. Centralised care is usually provided by doctors and nurses with specialist training in MDR-TB management. It also includes treatment and care provided by 'centralised outpatient clinics' i.e. out-patient facilities which are located at or near to the site of the specialised, central facility.

Additional definitions:

- *Directly observed therapy (DOT):*
  A treatment program where a health worker, community volunteer or family member, routinely observes participants taking their anti-tuberculous drugs.[15]
- *Treatment outcomes:*
  MDR-TB treatment outcomes were defined according to standard WHO definitions.[10]

Research question

Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the following outcomes: treatment adherence, improved treatment outcomes, adverse reactions, acquired drug resistance, reduced patient costs and health service costs; compared to treatment and care provided solely by specialized drug resistant TB (DR-TB) treatment centres? (WHO PICO Question 2)

PICO framework

The PICO framework for this research question is as follows:

- Population: All patients commencing treatment for MDR-TB
- Intervention: Decentralised treatment and care, provided by non-specialised or periphery health centres, by community health workers, community volunteers or treatment supporters. Treatment and care includes: DOT and patient support; administration of injectable antibiotics during the intensive phase; specialist care for co-morbidities (e.g. Human Immunodeficiency Virus (HIV) infection, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology)
- Comparator: Treatment and care provided solely by centralised and/or specialized DR-TB centres or teams.
- Outcomes: Adherence to treatment (or treatment interruption due to non-adherence); conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death; adverse reactions from TB drugs (severity, type, organ class); acquisition (amplification) of drug resistance; cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability); cost to health services

Methods

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses: guidance for reporting of systematic reviews and meta-analyses).[22]

Search terms

The authors developed and agreed on the comprehensive search terms in consultation with WHO counterparts. The search terms are listed in Table 1.

Table 2: Search terms applied using Medline search engine

Area	MeSH headings	Free text
Population	Tuberculosis, Multidrug-Resistant [MeSH]	((tuberculosis OR TB) AND (multidrug-resistan* OR multidrug resistan* OR multi-drug resistan* OR "drug resistan*" OR drug-resistan* OR multiresistan* OR "multi resistan*" OR "rifampicin resistan*" OR "extensively drug-resistan*" OR "extensively-drug resistan*" OR "extensively resistan*" OR MDR OR XDR OR TDR)) OR MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR "MDR TB" OR "XDR TB" OR "TDR TB"
Intervention		(directly observed OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment) AND (community OR outpatient OR public participation OR community-based OR decentralized OR non-specialized OR perhiph* health centres OR home-based OR ambulatory OR clinic OR community OR community health worker OR CHW OR volunteer*)

Population terms were combined using the Boolean operator "OR". Intervention terms were combined using "OR". Population and intervention term groupings were then combined using "AND". Comparator and outcome terms were not included in the search strategy, as a sufficiently small number of hits were achieved using only the population and intervention terms. By sifting for comparator and outcome during the manual sift, the likelihood of missing a potentially relevant paper was reduced.

Search sources and limits

We searched electronic health care databases, evidence based reviews, and hand searched the "grey literature". Search terms in Table 2 were adapted to the requirements of each database (see Annex 1).

Sources searched to identify relevant literature are detailed in Table 3. Each search was limited to publications from 1995-onwards, given that this is the time-frame in which DOT for TB has been widely used. Searches were not restricted by language, publication type or study design.

Table 3: Information sources searched to identify relevant literature

Category	Sources
Healthcare databases	MEDLINE EMBASE LILACS Web of Science Google scholar
Evidence based reviews	Cochrane library (includes CENTRAL, DARE, HTA, CDSR)
Grey literature	OpenSIGLE International Union of Tuberculosis and Lung Disease conference electronic abstract database
Unpublished studies	ClinicalTrials.gov WHO portal of clinical trials Consultation with expert in the field

Eligibility criteria for studies

The following inclusion and exclusion criteria were applied to the searches:

Inclusion criteria

- *Types of participants:*
  Studies recruiting individuals of all ages with MDR-TB.
  - » Given the limited availability of microbiological confirmation of MDR-TB in some settings, MDR-TB was defined as microbiological (phenotypic or genotypic) evidence of MDR-TB or, a clinical diagnosis of MDR-TB
  - » Studies which included individuals with XDR-TB or totally drug resistant (TDR-TB) were included
- *Types of interventions*:
  Studies including any of the following interventions (or any similar intervention but named differently): decentralised treatment and care provided by non-specialised or peripheral health centres, by community workers, community volunteers or treatment supporters.
  - » Treatment and care includes: DOT and patient support, injection during the intensive phase, and specialist care for co-morbidities (e.g. HIV, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology).
  - » No restrictions were placed on the timing of the intervention within the treatment period e.g. whether the intervention occurred in the intensive phase, continuation phase or throughout the treatment period.
- *Types of studies*:
  The following study types were included: randomized controlled-trials, prospective cohorts, retrospective cohorts, case control studies including at least 10 patients, or modelling studies
- *Types of comparators:*
  Treatment and care provided solely by specialist DR-TB centres or teams
- *Types of outcome measures:*
  Studies including one or more of the following outcome measures: adherence to treatment (or treatment interruption due to non-adherence); conventional TB treatment outcomes: cured/completed, failure, relapse, survival/death; adverse reactions from TB drugs (severity, type, organ class); acquisition (amplification) of drug resistance; cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability); cost to health services

Exclusion criteria

- Any study that did not report one or more of the above-stated outcomes of interest
- Any study reporting solely on primary outcomes of interest without a control/comparator group.
- Narrative reviews and commentaries/editorials
- Number of enrolled subjects in the intervention arm <10

For studies that were in a language other than English, we consulted an individual fluent in that language for interpretation and translation.

For studies where only an abstract was available, the study authors were contacted to obtain additional study information. Contactable, consenting authors were asked to complete a data collection form, specifically designed for this review, to obtain relevant study data.

Study selection and data extraction

In the first stage of study selection, titles and abstracts of papers identified from the above search were screened independently by two reviewers (JH and AB), for suitability for subsequent full text review.

In the second stage of study selection, full-text papers identified from the first stage were reviewed independently by two reviewers (JH and AB). A standardised extraction form was developed and pilot tested. Two reviewers (JH and GF) independently extracted the data from the papers selected for final inclusion. Data were compared, and unresolved disagreements in study selection or extraction were resolved consensus. An additional search of reference lists of all included articles, a search of all articles citing included articles, and review articles related to the research question were also conducted, to identify any further articles eligible for inclusion. For studies where interim findings were reported in one paper, and then more completely in a subsequent paper, the latter was selected for review inclusion. Study authors were contacted to clarify or obtain missing data where necessary.

Data extracted included: study design; study objective; study population characteristics (sample size, method of diagnosing MDR-TB, HIV prevalence, co-morbidities); details of intervention (organisation initiating decentralised care, method of selection of intervention group, time period intervention occurred, treatment regimen, nature of DOT, provider and location of treatment, duration/timing of decentralised treatment, additional support provided); details of control group (derived from the same population and/or same time period); event numbers for each outcome measure (as detailed above under "Types of interventions" in the Inclusion Criteria, above).

Study quality assessment

Risk of bias was assessed using the Newcastle Ottawa Scale for assessing the quality of nonrandomized studies[23] and the GRADE methodology.[24]

Analysis

A meta-analysis of relative risk and 95% confidence intervals for each treatment outcome, where sufficient studies (3 or more) were identified, comparing the intervention to the comparator group, were calculated using a generalised linear mixed model with study as a random effect, using RevMan 5.2. Forest plots summarised the data for individual trials. Outcomes were estimated as pooled proportions using the exact binomial method.[25] For each comparison, an I2 statistic was calculated to evaluate heterogeneity between studies.

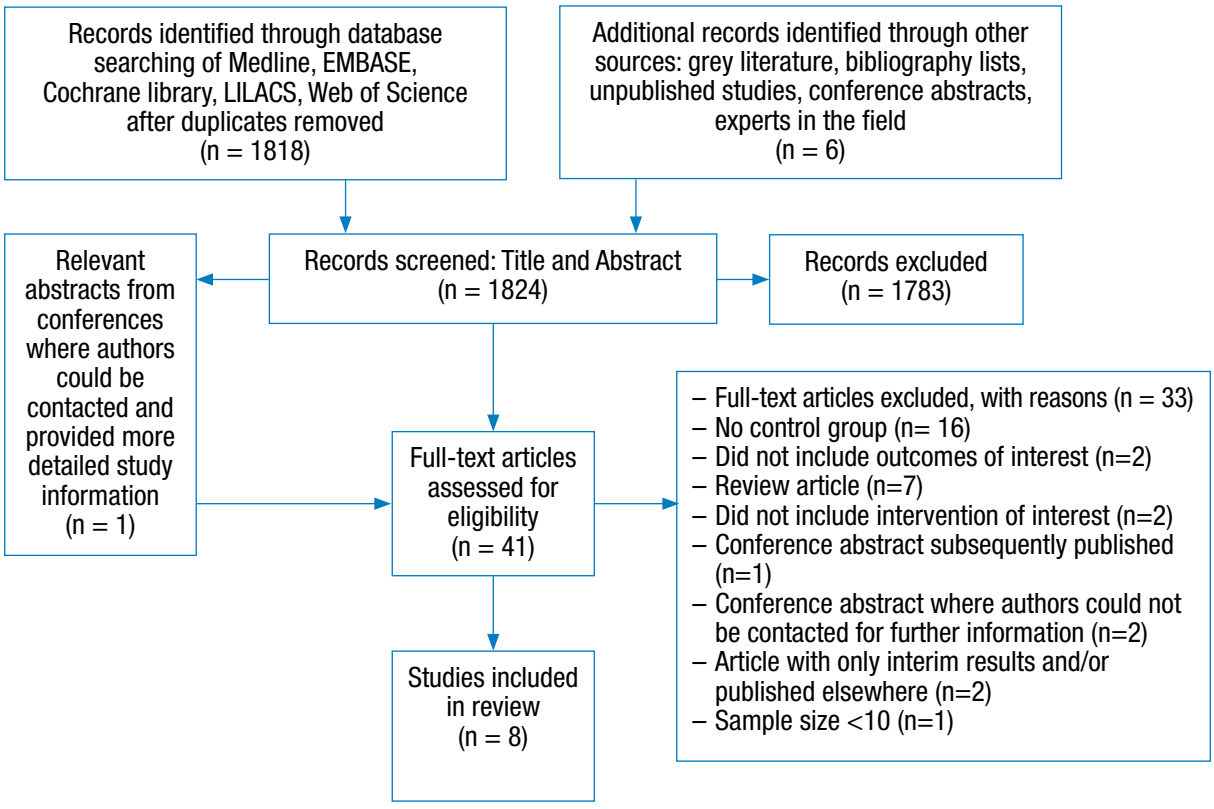
[26, 27] Where there were sufficient studies (five or more with the same end-point),[28] publication bias was assessed by funnel plot. Where available, costings were converted to $US 2015, based upon published World Bank conversion rates. Where insufficient studies were available to perform a meta-analysis, or where substantial heterogeneity precluded meta-analysis, we presented a table of findings of individual included studies. Statistical analysis was performed using SAS 9.3 (Cary, NC, USA). Forest plots of proportions were created using R version 3.2.5. An assessment of the overall study outcomes were performed using the GRADE methodology and summarized using GRADEPro software.

Results

Search results

The database search identified 1818 non-duplicate records. An additional six records were identified from searching conference abstracts (two) and bibliography lists of relevant papers (four). The title and abstract of 1824 records were reviewed identifying 41 articles for full-text review. Of these, 33 did not meet the inclusion criteria (see Figure 1 and Annex 2 for reasons for exclusion), leaving eight eligible studies (one unpublished) for review inclusion. [13, 29-35] Figure 1 shows the flow of search results and selection of eligible studies. The search was performed in January 2016.

Figure 1: Diagram of search results for eligible studies included in review of decentralised care of MDR-TB, compared to centralised care.



Findings

Key characteristics of the eight included studies are presented in Table 3. Of these studies, which included 4,493 patients with MDR-TB, two were performed in high income countries - Taiwan and the United States. The remainder were from low and middle income countries - South Africa, Swaziland, the Philippines and Nigeria. Two studies modelled cost-effectiveness, whilst the remaining six were cohort studies and reported on treatment outcomes (six) and/or cost of health-care (one). Of the studies that reported on treatment outcomes, five evaluated treatment success, four - loss to follow-up, four – death, and three - treatment failure. There were no randomised controlled trials evaluating decentralised MDR-TB treatment and care. Decentralised care described in the different studies included both home-based and decentralised clinic-based care. In one study, decentralised care occurred in a rural hospital.[32] In all except for one study, centralised care occurred in a specialised hospital. The (unpublished) study by Kerschberger et al [35] compared home-based DOT by trained community volunteers to a control cohort of clinic-based care by nurses. Based on a consensus of reviewers, this study was judged to be eligible for review inclusion given that the intervention provided decentralised care aimed to overcome the limitations of the existing treatment program which was clinic based care. Most decentralised and centralised management approaches used DOT. Importantly, patient selection for decentralised care was not randomised in any of the included cohort studies. Instead, treatment allocation was based upon patient factors likely to make centralised care more difficult or less successful e.g. residential location far from a centralised facility. No studies reported on treatment adherence, the acquisition of drug resistance or treatment costs for individual patients.

Pooled treatment outcome estimates

Table 4 shows the results of the pooled estimates for treatment outcomes. There were five studies which evaluated treatment success. The pooled relative risk (RR) from these five studies showed improved treatment success with decentralised compared to centralised treatment - pooled RR = 1.13 (95% CI 1.01-1.27). Pooled proportions of studies evaluating treatment success for decentralised and centralised care were 67.3% (95%CI: 53.8-78.5%) and 61.0% (95%CI: 49.0-71.7%) respectively. The pooled analysis of the four studies evaluating loss to follow up for MDR-TB patients showed a trend towards reduced loss to follow up with decentralised versus centralised care – pooled RR = 0.66 (95%CI 0.38-1.13). Pooled proportions of studies evaluating loss to follow-up for decentralised and centralised care were 11.9% (95%CI: 5.7-23.3%) and 18.0% (95%CI: 9.3-31.8%) respectively. The pooled RR from the four studies which evaluated death with decentralised, compared to centralised treatment was 1.01 (95% CI: 0.67-1.52). Pooled proportions of studies evaluating death for decentralised and centralised care were 17.8% (95%CI: 15.9-19.9%) and 18.6% (95%CI: 14.5-23.6%) respectively. The three studies evaluating treatment failure resulted in a pooled RR of 1.07 (95%CI 0.48-2.40) for decentralised versus centralised care. Pooled proportions of studies evaluating treatment failure for decentralised and centralised care were 4.2% (95%CI: 1.4-11.9%) and 4.3% (95%CI: 2.3-8.1%) respectively. There was considerable heterogeneity observed between studies. Figure 2 shows forest plots of these four outcome measures for

decentralised versus centralised MDR-TB treatment and care. Figure 3 shows a forest plot of proportions for treatment success. Owing to the small number of eligible studies, we did not formally assess publication bias.

Sensitivity analysis (analysis excluding Narita *et al*) for treatment outcomes

Of the studies eligible for review inclusion, the study by Narita *et al*[13] differs from the other studies with respect to: the income level of the country (high income versus predominantly low income), the years in which the intervention was conducted (1990s versus 2000s), the small sample size and the method of selection into the intervention and control groups (patients were selected for specialised TB hospital care if they were failing treatment or non-adherent) (Table 3). The results for treatment success and death for this study differ significantly from the other studies, and have wide confidence intervals (forest plots in Figure 2 and 3). Due to the marked heterogeneity of this study compared to the other included studies, we compared pooled proportions and relative risk estimates of the studies reporting on treatment success and death, with and without inclusion of the Narita *et al* study (Table 5). There was no significant difference in these estimates when this study was or was not included in the analysis. The study by Narita *et al* did not report treatment failure or loss to follow-up.

Treatment costs

Of the eight studies eligible for review inclusion, three (two modelling[33, 34] and one cohort study[35]) reported on treatment costs. Table 6 compares the treatment cost to the health-care system for one MDR-TB patient in the decentralised and centralised setting. The two modelling studies showed significant cost savings using a decentralised compared with a centralised model. Whereas, the study by Kerschberger *et al[35]* showed similar treatment costs for both treatment models.

Methodological quality of included studies

Table 4 and 7 shows the risk of bias assessment for the six included studies (excluding modelling studies). In all studies, a non-random method was used to select the intervention and control cohorts. In four of the six studies, the patients were chosen for decentralised treatment based on patient factors, such as residential location, socio-economic factors and risk factors for loss to follow-up. In the remaining two studies, treatment of the intervention and control groups occurred consecutively (not concurrently) reflecting the implementation of a new decentralised treatment program. Heterogeneity (inconsistency) was observed for all treatment outcomes, as indicated by the high I^2 values (from 74 to 88%) for pooled RR estimates. For all treatment outcomes, except for treatment success, there were wide variances in the point estimates (Figure 2). These risk of bias and heterogeneity factors reduced the overall quality of the evidence (rated as very low) for all treatment outcomes (Table 4).

Uncontrolled studies

Table 8 shows a summary of the key characteristics for the studies evaluating treatment outcomes using decentralised care for MDR-TB, which do not have a control group. Our search found 16 such studies where decentralised treatment alone, without direct comparison to centralised treatment, was evaluated. Although these studies did not met the eligibility criteria for review inclusion, this summary has been included to provide additional information to the studies which were eligible for review inclusion, and includes all of the more recent studies compared to the last systematic review on this subject.[12]. We excluded one study[36] from the pooled analysis that reported on treatment outcomes of MDR-TB patients treated in a field hospital after an earthquake, as this unique study setting is not representative of routine programmatic conditions.

(i) Treatment outcomes

Table 9 shows the event frequency and pooled proportion estimates for the studies that reported on treatment outcomes. Included in this table for comparison, are the pooled proportions for the studies in this review which did include a control group, and also data from an individual patient data meta-analysis (9,153 patients from 32 observation studies) of MDR-TB treatment outcomes.[37]. The latter serves as a comparison of the pooled results from the uncontrolled studies of MDR-TB treatment, in a decentralised setting, with a 'control' group - studies evaluating MDR-TB treatment in a non-specific setting (this may include both decentralised and centralised care models). Figure 4 shows the forest plots of proportions for treatment success of the studies evaluating decentralised care for MDR-TB, without a control group.

(ii) Adverse events from TB medications

There were no studies eligible for review inclusion (i.e. included a control group), that evaluated adverse events associated with TB medications. Of the 16 uncontrolled studies, nine studies reported on adverse drug events. Table 10 shows the adverse event frequency (any adverse event, severe adverse event or any adverse event requiring discontinuation of therapy) and pooled proportion estimates for these studies.

Strengths and weaknesses of this review

The results of this review are based on comprehensive database and other information source searching. This review had strict eligibility criteria which only permitted studies which directly compared intervention and control cohorts from the same study population to be included. This substantially reduced the risk of bias due to indirectness, and is a defining feature of this review compared to other systematic reviews on this subject. However, including only studies with both an intervention and control group reduced the final number of included studies and potentially reduced the precision of the estimates. In addition there was an absence of data for a number of *a priori* outcomes of interest. Substantial heterogeneity was also observed between included studies. This likely reflects the important differences between the study settings and the specific interventions used in each setting. We addressed

the limitation of the small number of eligible studies by presenting additional data from studies on decentralised care for MDR-TB that did not include a control group. W

Authors conclusions

In conclusion, this review demonstrated that treatment success for MDR-TB patients improved with decentralised care. Loss to follow-up was also reduced with decentralised models of care, although the confidence limits crossed the null. No difference was seen between the rate of death or treatment failure between these two groups.

These findings are consistent with previous systematic reviews.[11, 12]. Given the diversity of each setting in which MDR-TB patients are managed (e.g. cultural and socio-economic differences and the availability of infrastructure and personnel), heterogeneity of decentralised care amongst different studies is to be expected. This underpins the importance of further research in different settings. As national TB programs from TB endemic countries throughout the world increasingly adopt decentralised approaches for managing patients with MDR-TB, careful and thorough reporting of program interventions and outcomes (e.g. using 'before and after' or stepped-wedge study designs) should be undertaken out so that the benefit of such interventions can be accurately determined and reported.

Finally, whilst a decentralised approach to MDR-TB management may improve treatment outcomes at the level of the population, management of each patient with MDR-TB should be tailored, where possible, to the individual's requirements and circumstances. Clinicians and health services will need to tailor policies to maximise treatment outcomes, and minimise socioeconomic hardship. Thus, TB treatment programmes should aim for a combination of available treatment models, in order to serve the needs of all patients.

Declaration of interests

The review authors have no financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the review.

Acknowledgements

The authors will like to acknowledge Dr Linh Nhat Nguyen (WHO) for his support with this review, and the USAID for their funding support.

Table 4: Key characteristics of included studies in systematic review of decentralised versus centralised treatment for MDR-TB

Author; Year; Country	Study design	Year of inter-vention	Sample size: inter-vention, control	HIV prevalence in study population	Description of control arm	Description of inter-vention arm	Method of selection of intervention group	Timing of intervention within TB treatment	Intervention and control: concurrent or consecutive	Outcomes measured
Loveday;[32] 2015; South Africa (KwaZulu-Natal)	Prospec-tive cohort	2008-2010	736, 813	75%	Treatment in central specialised TB hospital	Treatment in rural hospital followed by outpatient DOT (home or clinic based) by health workers	Based on residential location	Intensive phase	Concurrent	Treatment success Death Loss to follow-up Treatment failure
Chan;[29] 2013; Taiwan	Prospec-tive cohort	2007-2008	290, 361	0.9%	Hospital and out-patient clinics	Home based DOT by 'observers' and nurses	Time period	Entire duration of treatment	Consecutive	Treatment success
Kersch-berger;[35] 2016; Swaziland	Prospec-tive cohort	2008-2013	157; 298	81%	Clinic based care (patients visited nearest health facility daily)	Home based DOT by trained community volunteers	Based on residential location and socio-economic status	Intensive phase	Concurrent	Treatment success Death Loss to follow-up Treatment failure Cost to health care
Narita;[13] 2001; US (Florida)	Retro-spective cohort study	1994-1997	31,39	44.3%	Treatment in specialised TB hospital	Outpatient therapy (DOT and/or SAT)	Selected for control if: failing treatment, needed treatment of other medical condition, non-adherent	Entire duration of treatment	Concurrent	Treatment completion Death
Gler;[31] 2012; Philippines	Retro-spective cohort study	2003-2006	167, 416	Not stated	Treatment in central hospital	Community based DOT by trained health care workers.	Time period	After sputum culture conversion	Consecutive	Loss to follow-up
Cox;[30] 2014; South Africa (Khaye-litsha)	Retro-spective cohort study	2008-2010	512, 206	72%	Hospital based care	Community based care integrated into existing primary care TB and HIV services.	Based on residential location	Entire duration of treatment	Consecutive	Treatment success Death Loss to follow-up Treatment failure
Musa;[33] 2015; Nigeria	Mod-elling study	N/A	N/A	Not stated	Hospital based care	Home based DOT by trained health-care providers	Random selection	Intensive phase	N/A	Cost to health-care
Sinanovic;[34] 2015; South Africa (Khayelitsha)	Mod-elling study	N/A	467 total	72%	Fully hospitalised model (stay in hospital until culture conversion)	1 fully decentralised model (in primary health care clinics); 2 partially decentralised models	N/A	Entire duration of treatment	N/A	Cost to health-care

DOT = directly observed therapy; TB = tuberculosis; HIV = human immunodeficiency virus; SAT = self-administered therapy; MDR = multi-drug resistant; N/A = not applicable
Intensive phase defined by inclusion of an injectable antibiotic in the treatment regimen

Table 5: GRADE table of included studies in systematic review of decentralised versus centralised treatment for MDR-TB, showing pooled estimates for treatment outcomes and quality assessment of studies

Quality assessment							No of patients		Effect Estimate			
No of studies	Design	Limi-tations*	Inconsistency**	Indirect-ness***	Imprecision ****	Other	Decentralised care N events/N patients (pooled proportion, 95% CI)	Centralised care N events/N patients (pooled proportion, 95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Qua-lity	Impor-tance
Treatment Success vs Treatment Failure / Death / Loss to Follow-Up												
5	Obser-vatio-nal Studies	Serious con-cerns	No con-cerns	No con-cerns	No con-cerns	None	1035 / 1695 (0.67, 0.54-0.79)	979 / 1710 (0.61, 0.49-0.72)	1.13 (1.01-1.27)	74 more per 1,000 (from 6 more to 155 more)	⊕◯◯◯ VERY LOW	CRITICAL
Loss to Follow-Up vs Treatment Success/ Treatment Failure / Death												
4	Obser-vational Studies	Serious con-cerns	Serious con-cerns	No con-cerns	No con-cerns	None	278 / 1549 (0.12, 0.06-0.23)	384 / 1727 (0.18, 0.09-0.32)	0.66 (0.38-1.13)	76 fewer per 1,000 (from 29 more to 138 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Death vs Treatment Success / Treatment Failure / Loss to Follow-Up												
4	Observa-tional Studies	Serious con-cerns	Serious con-cerns	No con-cerns	No con-cerns	None	250 / 1405 (0.18, 0.16-0.20)	232 / 1349 (0.19, 0.15-0.24)	1.01 (0.67-1.52)	2 more per 1,000 (from 57 fewer to 91 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment Failure vs Treatment success / Death / Loss to Follow-Up												
3	Observa-tional Studies	Serious con-cerns	Serious con-cerns	No con-cerns	No con-cerns	None	90 / 1382 (0.04, 0.01-0.12)	55 / 1311 (0.04, 0.02-0.08)	1.07 (0.48-2.40)	3 more per 1,000 (from 22 fewer to 59 more)	⊕◯◯◯ VERY LOW	CRITICAL

* Limitations - All of the studies were observational studies.
The method of allocating patients to intervention and control groups was not randomised.

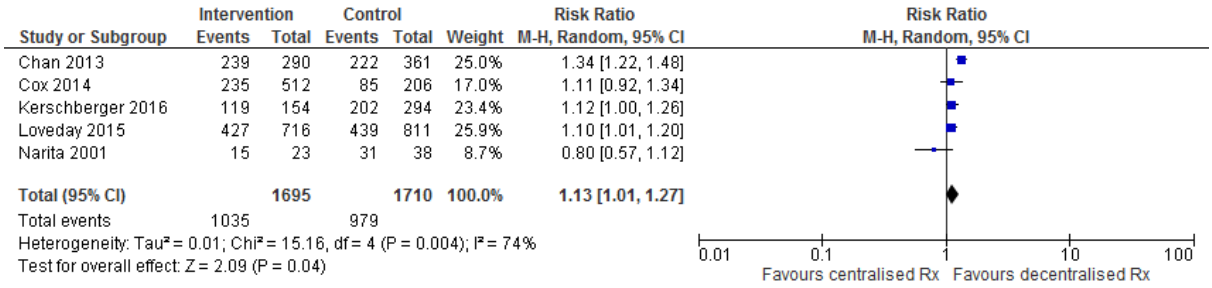
** Inconsistency - Based on estimated I^2

*** Indirectness – the study interventions and outcomes were directly relevant to the objective of this review

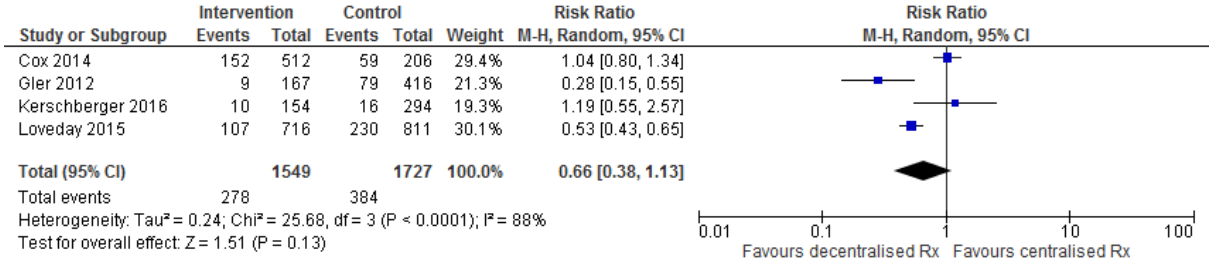
**** Imprecision – Based on 95% CIs

Figure 2:

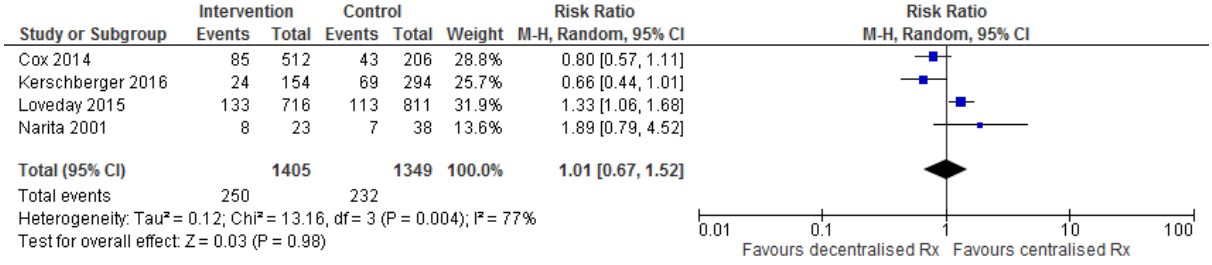
Forest Plot of Treatment Success for Decentralised versus Centralised MDR-TB treatment and care



Forest Plot of Loss to Follow-up for Decentralised versus Centralised MDR-TB treatment and care



Forest Plot of Death for Decentralised versus Centralised MDR-TB treatment and care



Forest Plot of Treatment Failure for Decentralised versus Centralised MDR-TB treatment and care

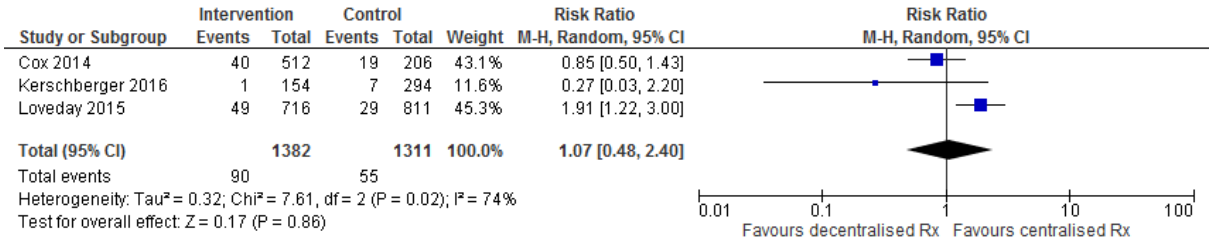
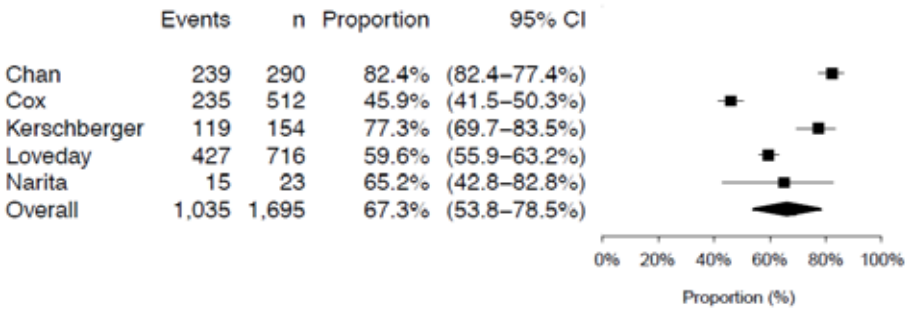


Figure 3: Forest plots of proportions for treatment success

(i) Decentralised treatment and care (intervention)



(ii) Centralised treatment and care (control)

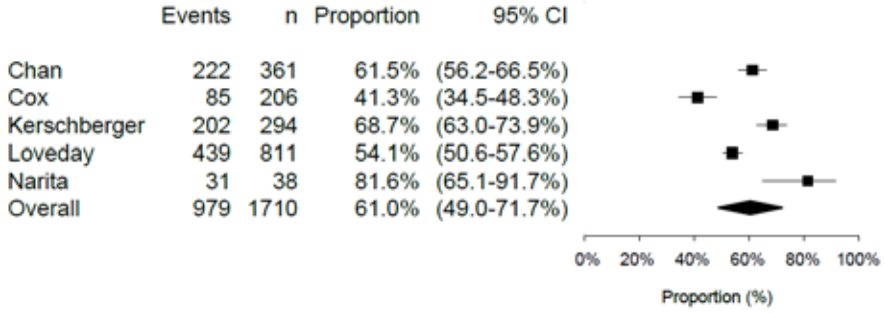


Table 6: Comparison of pooled proportion and relative risk estimates for studies evaluating treatment success and death, including and excluding Narita *et al[13]*

(a) Treatment success

Studies included in analysis	Studies (n)	Pooled proportion (95% CI) decentralised care	I^2	Pooled proportion (95% CI) centralised care	I^2	Pooled relative risk (95% CI) decentralised vs centralised care	I^2
Narita included	5	0.67 (0.54-0.79)	97.4%	0.61 (0.49-0.72)	93.4%	1.13 (1.01-1.27)	74%
Narita excluded	4	0.68 (0.52-0.63)	98.1%	0.57 (0.47-0.66)	92.8%	1.17 (1.05-1.30)	71%

(b) Death

Studies included in analysis	Studies (n)	Pooled proportion (95% CI) decentralised care	I^2	Pooled proportion (95% CI) centralised care	I^2	Pooled relative risk (95% CI) decentralised vs centralised care	I^2
Narita included	4	0.18 (0.16-0.20)	49.5%	0.19 (0.15-0.24)	82.3%	1.01 (0.67-1.52)	77%
Narita excluded	3	0.18 (0.16-0.20)	0.0%	0.19 (0.14-0.24)	88.3%	0.91 (0.59-1.42)	82%

Table 7: Treatment cost to the health-care system for one MDR-TB patient in the decentralised and centralised care setting (in US dollars)

Study	Study Design	Country	Description of decentralised care	Cost of decentralised care	Description of centralised care	Cost of centralised care
Musa[33] 2015	Modelling	Nigeria	Home-based care for entire duration of treatment	$1,535	Hospital-based care for intensive phase then home-based care for continuation phase	$2,095
Sinanovic[34] 2015	Modelling	South Africa	Primary health-care clinic for entire duration of treatment	$7,753	Hospital-based care for intensive phase (until 4 month culture conversion) then clinic based care	$13,432
Kerschberger [35] 2016	Retrospective cohort	Swaziland	Home-based care for entire duration of treatment	$13,361	Clinic-based care for intensive phase then home-based care for continuation phase	$13,006

Table 8: Risk of Bias Assessment[23] of Included Studies (excluding modelling studies)

Study	Selection (max = 4)	Comparability (max = 2)	Outcome (max = 3)	Total score[1] (max = 9)
Loveday 2015	3	0	3	6
Chan 2013	4	1	3	8
Kerschberger 2016	3	0	3	6
Narita 2001	2	0	3	5
Gler 2012	4	1	3	8
Cox 2014	3	0	3	6

[1] A higher score is associated with a lower risk of bias

Table 9: Key characteristics of the 16 studies on decentralised treatment and care for MDR-TB patients, without a comparator group

Author; year; country	Study design	Number receiving intervention	HIV prevalence	Description of intervention	Outcome measures reported	Overall findings/conclusion
Brust;[38] 2013; South Africa (KwaZulu-Natal)	Prospective cohort	91	81%	Home based care: nurses, CHWs, and family supporters trained to administer injections, provide adherence support, and monitor for adverse reactions.	Adverse events	In MDR-TB/HIV co-infected patients AE's to medications were common but most mild. Those on ART did not experience more AE's. Co-infected pts can be treated safely in a home-based setting
Brust;[39] 2012; South Africa (KwaZulu-Natal)	Prospective cohort	80	82.5%	Home based care: nurses, CHWs, and family supporters trained to administer injections, provide adherence support, and monitor for adverse reactions.	Treatment outcomes	Integrated, home-based treatment for MDR-TB and HIV may improve Rx outcomes in rural, resource-poor, high-HIV prevalent settings
Burgos;[4] 2005; US (San Francisco)	Retrospective cohort	48	23%	DOT was provided in the field by unlicensed public health personnel or at the clinic by an assigned nurse	Treatment outcomes; Adverse events Health-care cost	Treatment of MDR-TB in HIV negative patients as an outpatient is feasible and associated with high cure rates and lower cost than in other published studies. Patients with HIV infection had very poor treatment outcomes
Cavanaugh;[40] 2016; Bangladesh	Retrospective cohort	77	0%	Home based DOT by trained paraprofessionals who administer medications (including injections), and monitor for adverse events.	Adverse events (documentation versus patient interview recollection)	The programme appears to be feasible and clinically effective however there is inadequate monitoring of adverse events
Charles;[36] 2014; Haiti	Retrospective cohort	110	25%	Field hospital established after the hospital was destroyed in the earthquake for the management of MDR-TB patients in Port-au-Prince.	Treatment outcomes	Good outcomes for MDR-TB patients in the field hospital setting despite the adverse conditions
Drobac;[41] 2005; Peru (Lima)	Retrospective cohort	38	6%	Community-based DOTS for children with MDR-TB	Treatment outcomes; Adverse events	Percentage cured in this community-based treatment program (94%) was at least as high as any reported for a referral hospital setting and was higher than that for adults enrolled in the DOTS program in Peru
Furin;[42] 2001; Peru (Lima)	Retrospective cohort	60	1.7%	Community-based DOTS	Adverse events	In young patients with little co-morbid disease, MDR-TB Rx rarely caused life-threatening adverse effects. Common side effects may be managed successfully on an out-patient basis
Isaakidis;[43] 2012; India (Mumbai)	Prospective cohort	67	100%	Community-based program for Rx of patients with HIV/MDR-TB co-infection	Adverse events	AE's occurred frequently in this MDR-TB/HIV cohort but not more frequently than in non-HIV patients on similar TB medications. Most AE's can be successfully managed on an outpatient basis through a community-based treatment program
Isaakidis;[44] 2011; India (Mumbai)	Prospective cohort	58	100%	Outpatient care for HIV/MDR-TB co-infected patients involving public-private ARV centres and a network of community NGOs	Treatment outcomes	Encouraging rates of survival, cure and culture conversion were found with this Rx program

Author; year; country	Study design	Number receiving intervention	HIV prevalence	Description of intervention	Outcome measures reported	Overall findings/conclusion
Malla;[45] 2009; Nepal	Prospective cohort	175	Not stated	DOT on an ambulatory basis through a decentralized network of clinics	Treatment outcomes	There were high MDR-TB cure rates in this ambulatory-based treatment programme
Mitnick;[46] 2003; Peru (Lima)	Retrospective cohort	75	1.3%	Community-based DOT	Treatment outcomes; Adverse events	There were high MDR-TB cure rates in this community-based treatment programme
Mohr;[47] 2015; South Africa (Khayelitsha)	Retrospective cohort	853	70.9%	Community-based Rx for DR-TB in the patient's nearest primary care clinic.	The impact of HIV and other factors on DR-TB treatment outcomes	Response to DR-TB treatment did not differ with HIV infection in a programmatic setting with access to ART
Satti;[48] 2012; Lesotho	Retrospective cohort	19	74%	Community-based Rx for children with MDR-TB	Treatment outcomes; Adverse events	Paediatric MDR-TB and MDR-TB/HIV co-infection can be successfully treated using a combination of social support, close monitoring by community health workers and clinicians, and inpatient care when needed
Seung;[5] 2009; Lesotho	Retrospective cohort	76	74%	Community-based DOT that included social and nutritional support	Treatment outcomes; Adverse events	This program was successful in reducing mortality in MDR-TB patients
Thomas;[49] 2007; India (Chennai)	Prospective cohort	66	Not stated	MDR-TB management under field conditions where DOTS programme has been implemented	Feasibility; Treatment outcomes; Adverse events	Rx outcomes in this program were suboptimal. The main challenge was identifying providers close to patient's residential location who were able to administer injections, and manage of drug AE's
Vaghela;[50] 2015; India (Delhi)	Prospective cohort	113	Not stated	Home based MDR-TB treatment and care with counselling support.	Treatment outcomes	Home based care with counselling support is an important intervention in management of MDR-TB patients

CHW = community health worker; MDR-TB = multi-drug resistant tuberculosis; HIV = Human Immunodeficiency Virus; AE = adverse event; DOT = directly observed therapy; DOTS= directly observed therapy short course; NGO = non-government organisation; TB = tuberculosis; DR-TB = drug resistant tuberculosis; ART = anti-retroviral therapy

Table 10: Event frequency and pooled proportion estimates for treatment outcomes of studies without a comparator group, evaluating decentralised treatment and care for MDR-TB patients. Included for comparison, are studies that do include a comparator group, and a meta-analysis of MDR-TB treatment outcome in a non-specific setting[37]

a) Treatment success (vs death, treatment failure, loss to follow-up)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	13	955	1,570	76.1%	62.7%	85.9%	97.0%
Decentralized [b]	5	1,035	1,695	67.3%	53.8%	78.5%	97.4%
Centralized [b]	5	979	1,710	61.0%	49.0%	71.7%	93.4%
Non-specific [c]	15	NR	4,637	64%	52%	76%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

b) Death (vs treatment success, treatment failure, loss to follow-up)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	13	228	1,570	11.8%	7.3%	18.3%	84.1%
Decentralized [b]	4	250	1,405	17.8%	15.9%	19.9%	49.5%
Centralized [b]	4	232	1,349	18.6%	14.%	23.6%	82.3%
Non-specific [c]	15	NR	4,637	8%	3%	12%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

c) Treatment failure (vs treatment success, death, loss to follow-up)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	12	85	1,526	3.0%	1.3%	6.5%	90.4%
Decentralized [b]	3	90	1,382	4.2%	1.4%	11.9%	93.7%
Centralized [b]	3	55	1,311	4.3%	2.3%	8.1%	87.0%
Non-specific [c]	15	NR	4,637	5%	1%	8%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

d) Loss to follow-up (vs treatment success, treatment failure, death)

MDR-TB treatment model	Studies (n)	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	13	300	1,570	6.1%	2.9%	12.4%	98.2%
Decentralized [b]	4	278	1,549	11.9%	5.7%	17.8%	98.1%
Centralized [b]	4	384	1,727	18.0%	9.3%	31.8%	97.0%
Non-specific [c]	15	NR	4,637	15%	8%	22%	NR

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

[b] Studies, which have both an intervention and control group, of decentralised care for MDR-TB

[c] An individual patient data meta-analysis of TB treatment outcomes for MDR-TB in a non-specific setting (this may include both decentralised and centralised treatment models)[37]

Figure 4 - Forest plots of proportions for treatment success of the studies evaluating decentralised care for MDR-TB without a control group

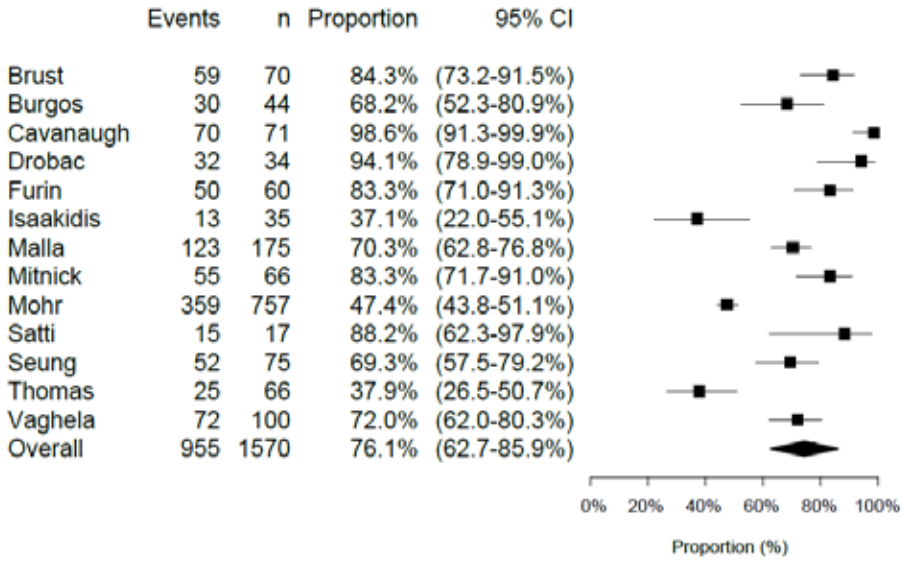


Table 11: Event frequency and pooled proportion estimates for studies evaluating decentralised care for MDR-TB, reporting on adverse events from TB medications

MDR-TB treatment model	Studies (n)	Outcome	Events	Total	Proportion (%)	Lower 95% CI	Upper 95% CI	I^2
Decentralized [a] (no control)	9	Any adverse events	410	521	86.3%	65.0%	95.6%	94.4%
Decentralized [a] (no control)	3	Severe adverse events	47	175	22.2%	7.4%	50.5%	92.1%
Decentralized [a] (no control)	8	Adverse events requiring discontinuation of therapy	76	445	7.4%	1.9%	25.0%	95.6%

[a] Studies, that do not include a control group, of decentralised care for MDR-TB

Appendixes

Appendix 1: Search terms used and reference retrieval success

Medline

URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: January 2016

1) Tuberculosis, Multidrug-Resistant [MeSH]
» OR
» ((tuberculosis OR TB) AND (multidrug-resistan* OR multidrug resistan* OR multi-drug resistan* OR "drug resistan*" OR drug-resistan* OR multiresistan* OR "multi resistan*" OR "rifampicin resistan*" OR "extensively drug-resistan*" OR "extensively-drug resistan*" OR "extensively resistan*" OR MDR OR XDR OR TDR)) OR mdrtb OR xdr tb OR mdrtb OR mdr-tb OR xdr-tb OR tdr-tb OR "MDR TB" OR "XDR TB" OR "TDR TB"

AND

2) ("directly observed" OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR "patient support")
» AND
» (community OR outpatient OR "public participation" OR community-based OR decentralized OR non-specialized OR "periph* health centres" OR home-based OR ambulatory OR clinic OR "community health worker" OR CHW OR volunteer)

1030 search results returned → title and abstract reviewed → 24 identified for full-text review

EMBASE

URL: http://www.embase.com
Search date: January 2016

1. Multidrug resistant tuberculosis.sh
2. (tuberculosis or TB).af
3. (multidrug-resistan* or multidrug resistan* or multi-drug resistan* or drug resistan* or drug-resistan* or multiresistan* or multi resistan* or rifampicin resistan* or extensively drug-resistan* or extensively-drug resistan* or extensively resistan* or MDR or XDR or TDR).af
4. 2 and 3
5. (MDRTB or XDRTB or TDRTB or MDR-TB or XDR-TB or TDR-TB or MDR TB or XDR TB or TDR TB).af
6. 1 or 4 or 5
7. (directly observed OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR patient support).af
8. (community OR outpatient OR public participation OR community-based OR

decentralized OR non-specialized OR periph* health centres OR home-based OR ambulatory OR clinic OR community health worker OR CHW OR volunteer).af.

9. 7 AND 8
10. 6 AND 9

1109 search results returned → title and abstracts reviewed → 18 identified for full text review → 10 relevant repeat studies from Medline search found (no additional studies found) and 2 relevant conference abstracts found

Cochrane Library including: Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Database of Systematic Reviews (CDSR)

URL: http://onlinelibrary.wiley.com/cochranelibrary/search/

Search date: January 2016

1. MeSH descriptor: [Tuberculosis, Multidrug-Resistant] explode all trees OR
2. ((tuberculosis OR TB) AND (multidrug-resistan* OR "multidrug resistan*" OR multi-drug resistan* OR "drug resistan*" OR drug-resistan* OR multiresistan* OR "multi resistan*" OR "rifampicin resistan*" OR "extensively drug-resistan*" OR "extensively-drug resistan*" OR "extensively resistan*" OR MDR OR XDR OR TDR)) OR (MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR "MDR TB" OR "XDR TB" OR "TDR TB")
3. #1 OR #2
4. ("directly observed" OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR "patient support") AND (community OR outpatient OR "public participation" OR community-based OR decentralized OR non-specialized OR "peripheral health centres" OR home-based OR ambulatory OR clinic OR "community health worker" OR CHW OR volunteer)
5. #3 AND #4

13 search results returned → no relevant reviews found

WHO portal of clinical trials

URL: http://apps.who.int/trialsearch/

Search date: January 2016

multi-drug resistant tuberculosis OR multidrug resistant tuberculosis OR multi drug resistant tuberculosis AND treatment (status=ALL)

64 records for 53 trials returned → no relevant studies found

LILACS

URL: http://lilacs.bvsalud.org/en/

Search date: January 2016

((MH: tuberculosis OR TB) AND (multidrug-resistan$ OR "multidrug resistan$" OR "multi-drug resistan$" OR "drug resistan$" OR drug-resistan$ OR multiresistan$ OR "multi resistan$" OR "rifampicin resistan$" OR "extensively drug-resistan$" OR "extensively-drug resistan$" OR "extensively resistan$" OR MDR OR XDR OR TDR)) OR MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR "MDR TB" OR "XDR TB" OR "TDR TB"

AND

(MH: "directly observed" OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR "patient support") AND (community OR outpatient OR "public participation" OR community-based OR decentralized OR non-specialized OR "periph$ health centres" OR home-based OR ambulatory OR clinic OR "community health worker" OR CHW OR volunteer)

7 search results returned → no relevant studies identified

Web of Science

URL: http://wokinfo.com/

Search date: January 2016

((Multidrug-Resistant Tuberculosis) OR ((tuberculosis OR TB) AND ((multidrug-resistan*) OR (multidrug resistan*) OR (multi-drug resistan*) OR (drug resistan*) OR (drug-resistan*) OR (multiresistan*) OR (multi resistan*) OR (rifampicin resistan*) OR (extensively drug-resistan*) OR (extensively-drug resistan*) OR (extensively resistan*) OR MDR OR XDR OR TDR)) OR (MDRTB OR XDRTB OR TDRTB OR MDR-TB OR XDR-TB OR TDR-TB OR (MDR TB) OR (XDR TB) OR (TDR TB))) AND ((directly observed OR DOT OR DOTS OR DOTS-Plus OR cb-DOTS OR treatment OR patient support) AND (community OR outpatient OR public participation OR community-based OR decentralized OR non-specialized OR peripheral health centres OR home-based OR ambulatory OR clinic OR community health worker OR CHW OR volunteer))

753 search results returned → title and abstracts reviewed → 19 relevant studies identified → Nil studies in addition to those from Medline identified

OpenSIGLE

URL: http://www.opengrey.eu/search/

Search date: January 2016

Multidrug-Resistant Tuberculosis OR ((tuberculosis OR TB) AND ((multidrug-resistan*) OR (multidrug resistan*) OR (multi-drug resistan*) OR (drug resistan*) OR multiresistan* OR (multi resistan*) OR MDR OR XDR) OR MDRTB OR XDRTB OR MDR-TB OR XDR-TB

No search terms used for intervention or outcomes.

76 search results returned → no relevant studies found

Google scholar

URL: https://scholar.google.com/

Search date: January 2016

multidrug resistant tuberculosis; community treatment

First 10 pages screened – 5 relevant studies identified. Nil studies in addition to those from Medline identified

International Union of Tuberculosis and Lung Disease conference electronic abstract database

URL: http://www.theunion.org/what-we-do/journals/ijtld/conference-abstract-books

Search date: January 2016

Hand searching of pdf's from the past 10 years (2006-2015) for abstracts related to MDR-TB and decentralised treatment.

2 relevant abstracts found → Author of 1 abstract contacted to obtain further information. Unable to contact the authors from the other abstract.

ClinicalTrials.gov

URL: https://clinicaltrials.gov/ct2/home

Search date: January 2016

multi drug resistant tuberculosis OR multi-drug resistant tuberculosis OR MDR TB OR MDR-TB

90 studies found → title and abstract reviewed → no relevant studies found

Review of reference lists from related review papers and from relevant papers identified from the database search → 1 additional study identified

Appendix 2: Full-text papers reviewed but excluded from review inclusion and reasons for exclusion

Reason for exclusion	References excluded from main analysis (N = 33)
No comparator group included in study	[4, 5, 36, 38-50]
Did not include outcomes in interest	[51, 52]
Review article (not an original study)	[6, 11, 12, 15-17, 21]
Did not include intervention of interest	[53, 54]
Conference abstract - subsequently published	[55]
Conference abstract - author uncontactable for further study information	[56]
Study published elsewhere	[57, 58]
Sample size <10 participants	[59]

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